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APPEARANCE OF A DENGUE-LIKE FEVER IN NORTHERN CALIFORNIA

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Late in the spring of 1934 a patient was seen in San Francisco who presented a clinical picture like that of dengue. A syphilitic patient inoculated with his blood showed the symptoms and signs of inoculation with dengue which have been studied experimentally in many parts of the world. Subinoculations in three other successive patients reproduced the same type of illness in each. As there are no recent reports of dengue occurring in the United States and as the disease has never been recorded as occurring endemically in Northern California, the possibility of its appearing here is of great importance. Although this is the only instance to date in which an attempt has been made to substantiate the diagnosis by inoculation into human subjects, five additional cases of apparently the same condition have been recognized. These endemic cases together with the four experimentally produced ones form the basis of this report.

REPORT OF CASES

CASE 1.—On the evening of April 30, 1934, I. A., a 41 year old insurance agent, married, was seen at his home complaining of a high fever of two days' duration.

The family history and the past history were irrelevant. His type of work required that he travel all over the state of California, and he was habitually careful of his water and food supply as a precaution against typhoid and other infections. A large police dog which was occasionally sick and had ticks and fleas was almost constantly with him. Nineteen days before the onset of the present illness he removed a tick from the cubital vein of his left arm while he was in Santa Clara County. Ten days later he was bitten twice by flies near Gonzales, and the next day, nine days before his present illness, he was bitten by a mosquito at Salinas, Monterey County.

Present Illness.—On the afternoon of April 28, while the patient was driving his car from San Francisco to Palo Alto, he noted that his back was a little stiff. He slept well that night, but at 8 o'clock the next morning he suddenly grew ill and thought that influenza was developing. He drove back to San Francisco and went to bed. At the onset he felt chilly, and his bones and joints ached all over. Pain in the back was severe, "like a hot poker" or "a sacro-iliac slip." His joints became stiff, the condition being "like arthritis"; his head ached moderately, and he felt feverish. He slept fairly well, but the next day he had severe pain in the right shoulder and excruciating pains and tenderness in the lower portion of the

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legs and in the heels. This was so pronounced that he could not stand up and had to crawl to the lavatory on his hands and knees. It felt "as if the marrow was being torn out of the bone." The temperature rose to 103 F. A chart of its course is shown in figure 1. The pulse rate varied proportionately.

On the third day the legs were better and the joints were no longer stiff but there were intense jabbing neuralgia-like pains which "felt like an ice-pick" in the right side of the face and in the right ear. These grew better on the fourth day, but the patient grew restless and irritable. On the fifth and sixth days he complained of severe prostrating headache, which was felt all through the head but was worse behind the eyes, and he had marked photophobia. He saw flashes

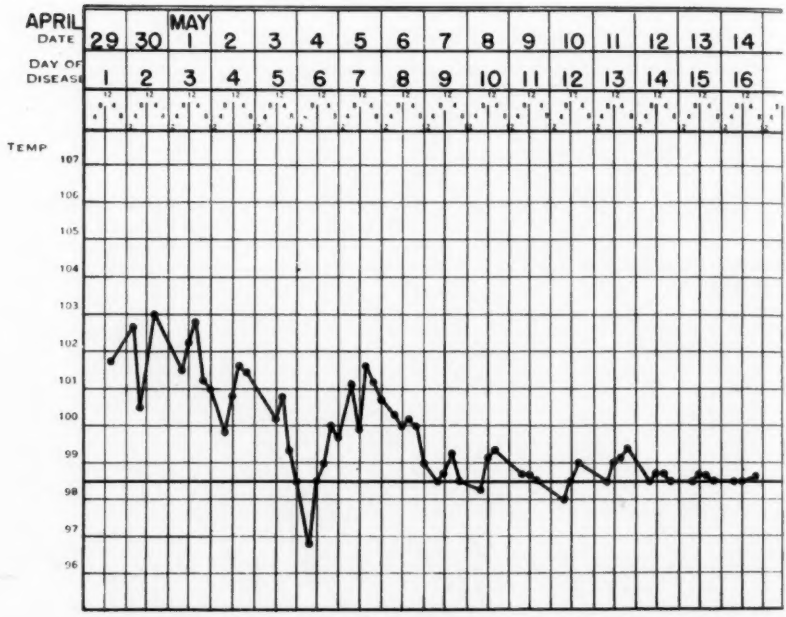

Fig. 1 (case 1).—Curve for temperature, showing biphasic form of fever.

of yellow light from time to time, as if an electric sign were turned on and off rapidly. Food had an appetizing smell but tasted bad, "like spoiled meat," and it was almost impossible for him to eat. He also had marked nausea, retching and distention and soreness in the upper part of the abdomen. There were pain and soreness in the testicles. During this time he complained of such severe itching of the hands, feet and lower portion of the legs that it was hard to keep him from scratching his skin deeply. Improvement occurred on the seventh day, and by the eighth day the patient was free from most of his troublesome symptoms.

Physical Findings During the Illness.—Examination on the evening of the second day disclosed no abnormalities except that the patient was flushed from the fever and had some tenderness of the muscles of the calves and of the heels. He was a large, well built man, was clear mentally and was not depressed or toxic.

The eyes, ears, nose, gums and throat appeared normal. The tongue had a thick creamy coating on the dorsal portion. The heart was not enlarged; the sounds were clear, and no murmurs were present. The lungs were normal. The abdomen showed no abnormalities except moderate tenderness at the left costal margin and in the epigastrium. There was marked tenderness in both lumbar regions. Although the patient complained of stiffness in the joints, particularly in those of the fingers, no signs of arthritis were present. No lymph glands were palpable in the neck, axillae or groins. The knee jerks and ankle jerks were present and equal. No cutaneous rash was present. The blood pressure was 120 systolic and 80 diastolic; the temperature was 102.8 F., and the pulse rate, 104. The bowels had moved regularly.

The findings were not materially altered until the fifth day, when there appeared frequent retching and vomiting, also tenderness and muscle spasm in the upper part of the abdomen which was most marked at the left costal margin. The face and neck became extremely flushed; the eyelids were puffy, and there was pronounced conjunctivitis. The patient was prostrated and irritable. He remained in this condition for three days and was slightly delirious on the second night. The neck was not stiff, and Kernig's sign was not present. The crushing headache was partially relieved by local pressure but was completely controlled only by opiates. On the eighth day there was much improvement, but the patient had a slight cough with a little thick, tenacious sputum. There were a few scattered râles at the base of the left lung but no signs of pulmonary infiltration. All unusual findings had disappeared by the next day except that the patient was weak and tired. There was no rash.

Laboratory Examinations.—Urine: The amount was scanty throughout the febrile period. There was only one voiding of about 100 cc. on the fifth day. The specific gravity varied between 1.024 and 1.032. The color was always high. No sugar was present. On the third day there was a light cloud of albumin, but on the fourth and sixth days the clouding was heavy. On the ninth and twelfth days a faint trace of albumin was found, and sixteen days after the onset of the illness there was no clouding. When large amounts of albumin were present the sediment showed a solid mass of hyaline and finely and coarsely granular casts occurring in such profusion that no estimate of the number could be made. Many white and red blood cells were also noted. By the sixteenth day only an occasional cast and a few cells were present.

Blood: On the third day there were 10,000 white cells, 72 per cent polymorphonuclears, 17 per cent lymphocytes, 7 per cent large mononuclears and 4 per cent transitionals. On the fourth day there were 7,000 white cells, 72 per cent polymorphonuclears, 22 per cent lymphocytes, 5 per cent large mononuclears and 1 per cent transitionals. The Schilling count showed that 57 per cent of the polymorphonuclears were banded and 43 per cent mature forms. Smears showed no malarial parasites on the fifth day. The sedimentation rate was 20 mm. in forty minutes. Cultures, including a special set-up for Brucella abortus, showed no growth. Agglutination tests were negative for Bacillus typhosus, Bacillus paratyphosus A and B, Brucella abortus of bovine, porcine and caprine strain and Bacterium tularense. The icteric index was 6 units.

On the sixth day the vomitus was greenish. The total acidity was 20. Free hydrochloric acid was absent. There was no occult blood. On the eighth day examination of the stool gave negative results for occult blood and for ova and parasites.

On the fourth day of this patient's illness 5 cc. of venous blood was withdrawn and oxalated, and one-half hour later injected into a vein of another patient

(case 2). A third patient (case 3) received a similar injection of 5 cc. of whole blood from the second patient, and a fourth (case 4) received 5 cc. of whole blood from the third patient. A fifth patient (case 5) was inoculated in a similar fashion with blood from the fourth patient but in this instance the blood was withdrawn on the third day of the illness instead of on the fourth day, as in the other three cases. Two other patients with chronic encephalitis received subcutaneous injections of 0.5 cc. of serum from the first patient (case 1) which had been kept in the icebox five days and seven days, respectively. Neither of them became ill or showed any significant change in temperature or pulse rate subsequently.

As the clinical course of dengue produced by inoculation is like that of the acquired type [1] and as the findings in the four cases of artificial

TABLE 1.—*Important Clinical Findings in the Six Cases of Endemic Dengue-Like Fever and in the Four Cases Produced by Inoculation of Whole Blood*

Clinical Findings	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Infection by inoculation	—	+	+	+	+	—	—	—	—	—
Sudden onset	+	+	+	+	+	—	+	—	+	+
Severe headache	+	+	+	+	+	+	—	+	+	—
Postorbital pain	+	+	+	+	+	+	—	+	—	+
Severe backache	+	+	+	+	+	+	+	+	+	—
Pains in the limbs	+	+	+	+	+	+	+	+	—	—
Stiffness of the joints	+	+	+	+	+	+	—	—	—	+
Photophobia	+	+	—	—	+	—	—	—	+	—
Perversion of the sense of taste	+	+	+	+	—	—	—	—	—	+
Suffusion of the face and neck	+	+	+	+	—	?	?	—	—	?
Herpes labialis	+	+	—	—	—	—	—	—	—	+
Vomiting	+	—	—	—	—	—	—	—	—	+
Severe abdominal pains	+	—	—	—	—	?	—	—	—	+
Enlargement of lymph glands	—	—	+	+	+	+	?	?	+	+
Enlargement of spleen	—	—	—	—	—	—	?	+	+	—
Pain in testicles	+	—	—	—	—		+	—	—	
Rash at onset	—	—	—	—	—	+	?	—	?	?
Terminal rash	—	+	+	—	—	—	—	—	+	—
Itching	+	—	+	—	—	+	—	+	—	—
Biphasic fever	—	—	—	+	—	+	?	+	+	+
Leukopenia	—	—	—	+	—	+	?	—	+	+
Duration of illness in days	8	8	6	9	??+	8	6	7	6	?8
Râles at bases of lungs	+	+	+	+	—	—	?	+	—	—
Jaundice	—	—	+	—	+	—	—	—	—	+
Albuminuria	+	+	?	—	—	—	?	—	—	—
Sequelae	—	+	+	—	+	+	—	+	—	+

infection closely resembled those in the endemic ones, the important symptoms and findings are recorded together for both groups in table 1, and detailed descriptions of the experimental series are omitted. The results of the white cell counts are listed in table 2 and shown graphically in figure 2. The four patients who were inoculated had syphilis of long standing; their blood showed strongly positive Wassermann and Kahn reactions, and they were hospitalized as possible candidates for malarial therapy.

CASE 2.—A. G. P., 50 years old Esthonian, single, had been hospitalized eight months previously on account of a stroke and partial loss of vision. He was inoculated on May 2, 1934, and ninety-two hours later there appeared fever, which lasted eight days. On the sixth day there developed an extensive macular rash over the shoulders and the entire trunk, which lasted six days. The "spots" varied in diameter from about 1 mm. to 1 cm. and were of a dusky red hue, gradually

fading out without any desquamation. As the curve for temperature is much like that observed in cases of so-called saddleback fever, it is shown in figure 3. After this attack of fever it was noted that the patient was quiet and drowsy for three weeks. He complained of photophobia and fulness and aching in the head and "sleeping twenty hours a day." His normally restless irritable disposition was in strong contrast to the present docile lethargic state. When allowed to lie in bed he slept almost constantly. After the first week he had daily rises of temperature

TABLE 2.—*White Blood Cell Counts in Nine Cases of Dengue-Like Fever*

Case No.	Day of Illness	White Cell Count	Differential White Cell Count, Percentage							
			Polymorphonuclears	Staff Cells	Segmented Cells	Lymphocytes	Transitional Forms	Large Monocytes	Eosinophils	Basophils
1	3rd	10,000	72	42	30	17	4	7	—	—
	4th	7,000	72	41	31	22	1	5	—	—
2	5th	7,800	70	—	—	30	—	—	—	—
	7th	8,400	64	34	30	30	—	4	2	—
	9th	16,350	40	10	30	50	1	6	3	—
	11th	15,900	45	12	33	46	5	4	—	—
	22nd	10,350	55	5	50	38	2	—	5	—
3	2nd	9,750	64	20	44	33	1	2	—	—
	3rd	11,800	75	30	45	25	—	—	—	—
	4th	16,000	84	60	24	15	—	1	—	—
	6th	23,350	81	45	36	18	—	1	—	—
	7th	30,000	77	51	26	21	—	2	—	—
	9th	18,700	85	—	—	15	—	—	—	—
4	2nd	4,350	53	37	16	40	1	6	—	—
	3rd	6,450	64	13	51	19	2	3	12	—
	4th	3,800	—	—	—	—	—	—	—	—
	5th	3,000	72	36	36	26	—	2	—	—
	6th	3,600	71	37	34	26	—	1	1	1
	7th	5,210	40	26	14	50	2	4	2	2
	9th	7,900	70	33	37	28	1	—	1	—
5	1st	10,250	57	21	36	41	—	2	—	—
	2nd	17,100	69	39	30	31	—	—	—	—
	4th	6,150	78	38	40	22	—	—	—	—
	5th	8,100	64	38	36	36	—	—	—	—
	7th	20,100	45	10	35	50	2	2	1	—
	8th	23,450	57	10	47	40	—	—	2	1
	11th	28,650	58	10	48	40	2	—	—	—
	13th	17,300	58	20	38	40	1	—	—	1
	15th	24,500	56	16	40	42	2	—	—	—
	18th	16,850	58	10	48	40	—	—	2	—
6	4th	8,000	72	—	—	26	—	1	—	1
	5th	6,350	50	—	—	50	—	—	—	—
	6th	5,400	—	—	—	—	—	—	—	—
	9th	5,800	—	—	—	—	—	—	—	—
8	4th	10,700	89	42	47	6	—	5	—	—
	7th	9,000	80	58	22	14	—	4	1	1
9	2nd	6,600	75	33	42	18	—	6	—	1
	3rd	4,250	67	35	32	27	—	4	1	1
	5th	4,900	55	26	29	41	—	4	—	—
10	10th	4,100	57	23	34	40	3	—	—	—

for two weeks from 99 to 100.5 F. and on one occasion to 101.6 F. The examination of the eyegrounds, general physical examination and neurologic examinations showed nothing unusual. On May 23, after the patient had been lethargic for ten days and febrile for three days, a lumbar puncture was performed. The fluid was clear and colorless, and the pressure was 255 mm. of water. There were 33 cells, all but 2 of which were lymphocytes, per cubic millimeter of fluid. There were 58 mg. of total protein and 59 mg. of sugar per hundred cubic centimeters. The Lange reaction was 0000000000. Three months previously the findings in the spinal fluid, including the Wassermann reaction, had been entirely negative. Thirty minutes after the puncture 3 cc. of spinal fluid was injected into the vein of a

volunteer. No reaction to this injection developed during one month of close observation. The patient gradually returned to his prefebrile state.

Case 3.—J. B., a 64 year old Greek, single, had been under observation in the hospital twice, a year previously, with a diagnosis of gastric crises with slight jaundice. He was inoculated on May 9, 1934, and ninety-six hours later the temperature rapidly rose to 102 F. It reached 104 F. on the third day and exceeded 103 F. during the next twenty-four hours. It gradually dropped to subnormal on the seventh day. On the sixth day there was a dusky mottling of the skin over the shoulders and trunk and the scleras were slightly icteric. The temperature was subnormal for two days, but marked tenderness and spasm developed in the right upper quadrant of the abdomen; the jaundice became intense, and the patient sank rapidly into a deep coma. The course of the icteric index is shown in

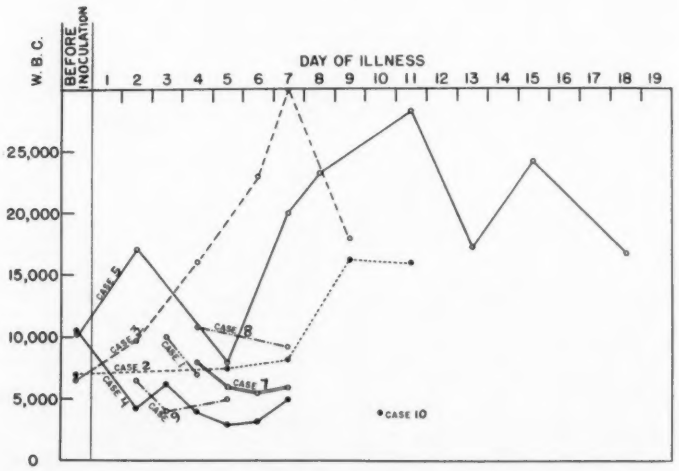

Fig. 2.—Course of the white blood cell counts in eight cases. In the only three (cases 2, 3 and 5) in which leukocytosis was present, the disease was produced by inoculation and was complicated by hepatitis in two and by encephalitis in one.

figure 4. Râles appeared in both lungs; on the third day after the attack of fever there was a terminal rise in temperature of 100 F., and the patient died.

Necropsy.—Macroscopic Examination: The body was that of a well nourished, markedly jaundiced man about 65 years of age. The upper jaw was edentulous. None of the superficial lymph glands were palpable. The thorax was of the emphysematous type. The heart was slightly enlarged, and there was dilatation of all the chambers. No lesions of the valves were found, but the coronary arteries showed many calcified atheromatous plaques, which markedly encroached on the lumens but did not produce complete occlusion. The arch of the aorta was normal in size, and its walls showed longitudinal wrinkling of the intima and a few atheromatous plaques and superficial ulcerations. Both lungs showed small old apical scars. A cut section showed marked congestion and edema, with many elevated consolidated hemorrhagic areas throughout but most marked in the lower lobes of both lungs. The bronchi were filled with frothy blood-tinged fluid.

The pleura and the pericardium were normal. The lower border of the liver extended 3 cm. below the right costal margin and 6 cm. below the xiphoid process. The liver measured 26 by 18 by 8 cm., and the surface was icteric and finely granular. The cut section was opaque. The gallbladder contained a few cubic centimeters of thin white fluid and 30 small black stones averaging 2 mm. in diameter. Its wall was thickened and the mucosa was replaced by fibrous tissue. No stones were present in the ducts. The spleen was of normal size, and was firm and smooth. The cut surface revealed congestion and prominent malpighian bodies. Examination of the pancreas, stomach and small bowel revealed nothing unusual. The large bowel was normal except for many small diverticula, which were most numerous in the transverse colon. Both kidneys were buried in fat. The capsules stripped easily. The surface showed a marked irregular granular

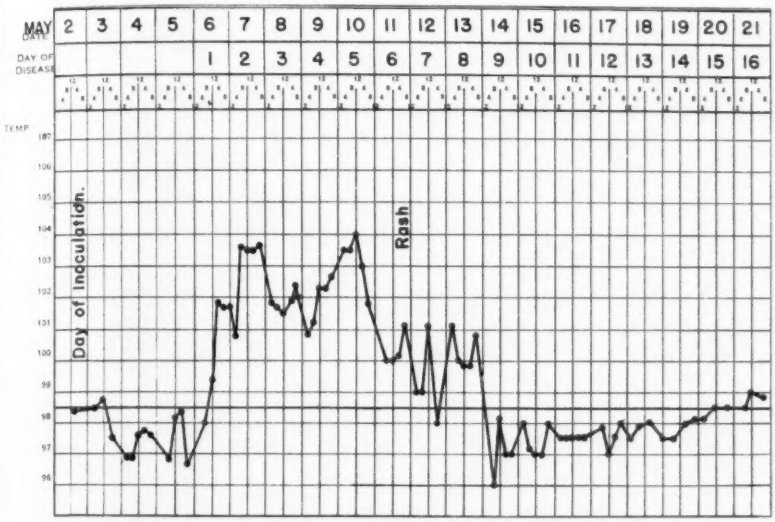

Fig. 3 (case 2).—Curve for temperature showing the characteristic abrupt onset of fever and its limited course. The disease was produced by inoculation with blood from I. A. (case 1).

appearance, and sections showed irregular areas of cloudy swelling. Both adrenal glands were normal except for congestion of the medulla. The urinary bladder and prostate were not remarkable. The brain was not examined.

Microscopic Examination: The heart showed many dense fibrous scars scattered throughout the myocardium. The media of the aorta was heavily infiltrated with round cells. Most of the alveoli of the lungs were filled with red blood corpuscles and a few polymorphonuclear leukocytes. Some of the alveoli contained many leukocytes and red cells enmeshed in fibrin. The liver cells (fig. 5) were separated from each other, and most of them had lost their nuclei except a few at the periphery of the lobules and near the capsule. Deeper in the liver only a few nuclei were to be seen. The cells stained poorly. Some of the cells about the central veins contained a small amount of brown granular pigment.

Some of the sinuses near the surface of the liver were filled with red blood cells but were only slightly dilated. The arteries showed a rather marked thickening of the intima, and there was an increase of fibrous tissue in the periportal regions and about the bile ducts. The bile ducts were lined by columnar epithelium which stained well but was detached and filled the lumen in most places. The capsule showed slight fibrous thickening.

A section stained with phyloxin (a carmine red dye used in 1 per cent solution) to bring out nuclear detail showed the remaining nuclei to contain acidophilic masses at the periphery of the nucleus. There was usually one, and sometimes there were two, of these masses, but nothing resembling inclusion bodies could be demonstrated. The Kupffer cells showed no changes.[1]

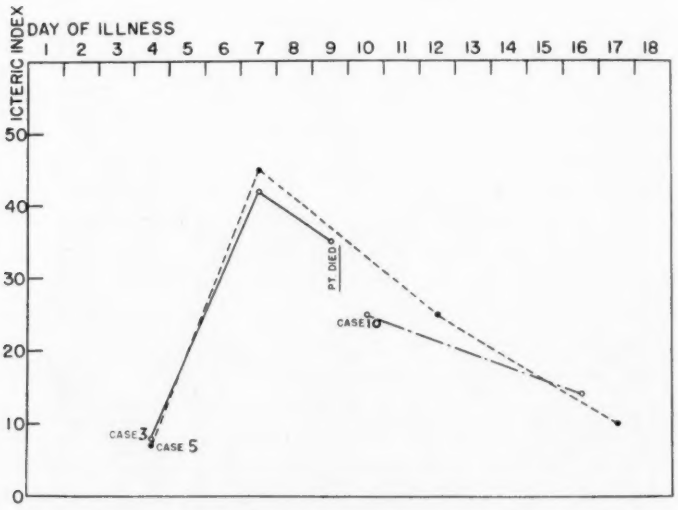

Fig. 4.—The course of the jaundice as measured by the icteric index in the three cases in which hepatitis occurred as a complication.

The walls of the gallbladder showed marked fibrous thickening with a few areas of round cell infiltration. Many of the pulp cells of the spleen were swollen and had lost their nuclei, but there was no evidence of necrosis. The renal cortex contained scars heavily infiltrated with round cells. Most of the epithelial cells of the convoluted tubules had lost their nuclei and were swollen and desquamated into the lumen. The tufts of some of the glomeruli were swollen and edematous and were moderately infiltrated with round cells and a few polymorphonuclear leukocytes. The arterioles showed a moderate fibrohyaline thickening of the intima. The sections of bone marrow showed a moderate increase in the extent of the reticular stroma and blood-forming cells. The sinusoids were filled with erythrocytes. Normoblasts were present in considerable numbers throughout the reticulum and were collected in rather extensive clusters at some points. Smears showed an increase in relative numbers of normoblasts, and mitotic figures were numerous.

1. Dr. James Owmby Jr. made special studies of the hepatic tissue.

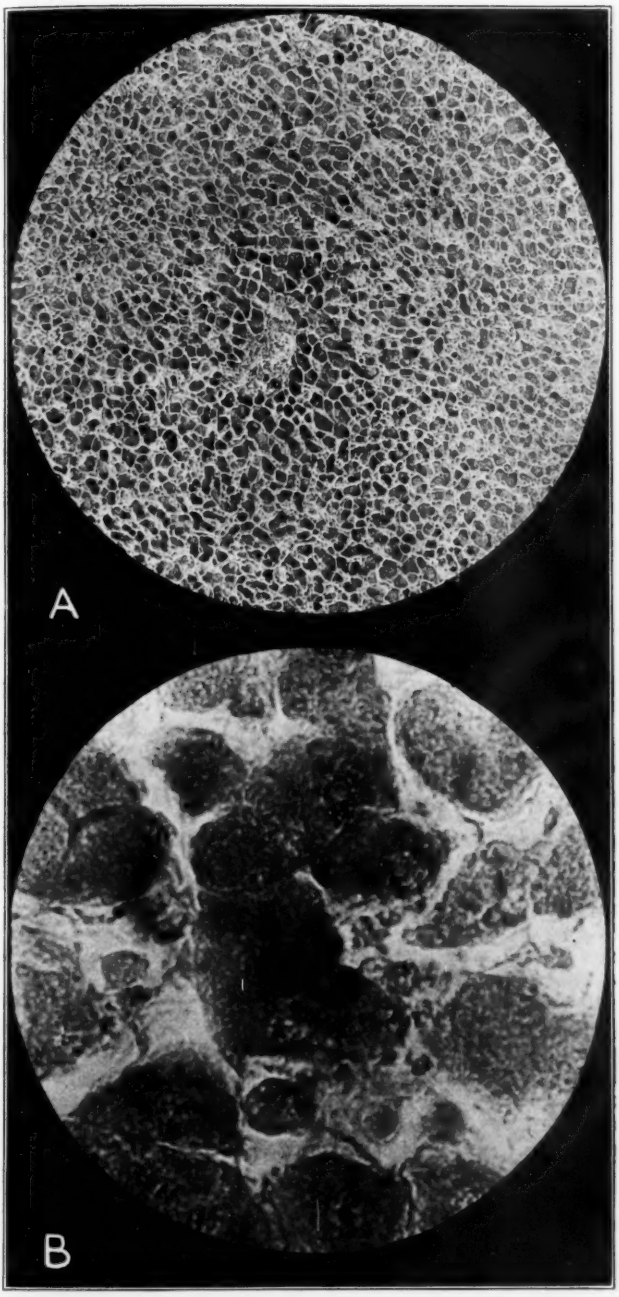

Fig. 5 (case 3).—Photomicrographs of a section from the liver: *A*, lower magnification (× 100) showing diffuse toxic necrosis; *B*, high magnification (× 800) showing loss of normal structure of hepatic cells, only an occasional nucleus remaining.

Leukocytic marrow cells were numerous and showed normal developmental forms. There was a relative numerical increase of leukocytes in the more mature stages. There was no evidence of any marked hyperplasia of leukocytic cells.

Anatomic Diagnosis.—The diagnosis was acute toxic necrosis of the liver, gallstones, chronic cholecystitis, bronchopneumonia, general arteriosclerosis, severe local arteriosclerosis of the coronary arteries, with scars in the heart, diverticulosis of the colon, syphilitic involvement of the aorta and hyperplasia of erythropoietic cells in the bone marrow.

Case 4.—W. D. B., a 63 year old English plasterer, divorced, had been under observation for eight months with clinical and roentgen evidence of Paget's disease and a broken-down gumma of the left shin. He received the inoculation on May 19, 1934, and eighty-eight hours later his temperature began to rise. In

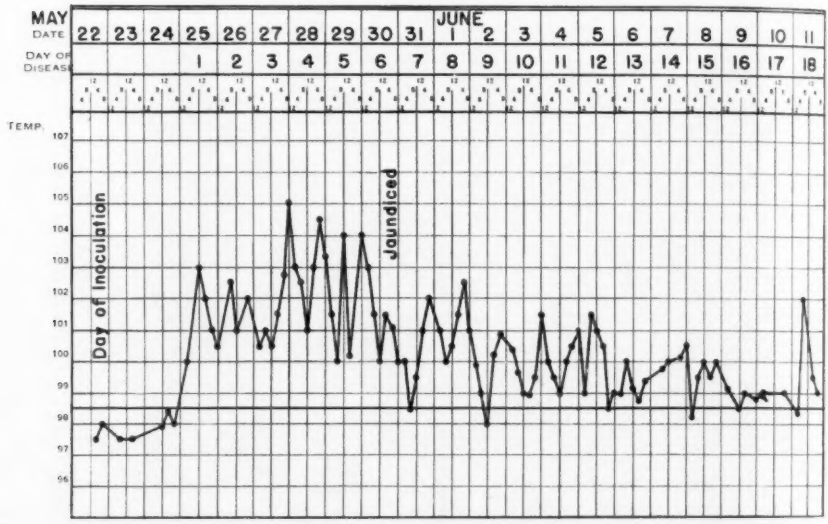

Fig. 6 (case 5).—Curve for temperature, showing a short period of incubation, high fever, jaundice and persistent pyrexia. The disease was produced by inoculation with blood from W. D. B. (case 4).

twelve hours it reached 103.5 F.; for the next twelve hours it remained at 103 F. or just above that level, and it then fell in four hours to 97.4 F. For the next eight days it rose and fell rapidly and irregularly between the normal level and 102 F. On the ninth day of the illness it dropped in eight hours from 101.8 to 98 F. and remained normal or subnormal thereafter except for one rise to 99 F. three days later. The patient insisted on being up and about during the latter part of the illness, and rapid improvement was noted.

Case 5.—L. H., a 60 year old German, single, had been under observation for three months with arteriosclerosis, hypertension, slight mental disturbance and changes in the cerebrospinal fluid indicative of syphilis of the central nervous system. He was inoculated on May 22, 1934, and sixty hours later the temperature began to rise. The course of the fever is shown in figure 6. The tempera-

ture fell to normal for the first time on the seventh day, which might represent the end of the usual course of the disease, but fever was present daily for two additional weeks; this seemed to be due to the complicating hepatitis. The scleras appeared yellow on the sixth day, and there was clinical evidence of jaundice for ten days in all, although the liver was not palpable and not tender. The course of the icteric index is shown in figure 4. The patient was allowed to be up and about after the fever subsided, and he seemed as well as previously. On the second day of this patient's illness blood was taken for inoculations into animals. Five mice were given intraperitoneal injections of 0.2 cc. of serum, and one guinea-pig received an intraperitoneal injection, and two others, intracerebral injections, of 0.3 cc. of serum. One rabbit was inoculated intracerebrally with a like amount of serum, and one Java monkey and one Macacus rhesus monkey were similarly inoculated with 1 cc. of serum each. In none of the animals did any recognizable symptoms develop.

The five patients whose illness is described were all infected with the same organism, and each was carefully observed throughout the clinical course of the disease. The five patients with similar manifestations which have since come under observation seemed to have the same disease, and in each instance no definite diagnosis of any commonly recognized condition could be established. The cases are reported as completely as possible.

CASE 6.—R. N., a 22 year old Japanese housewife, complained of generalized pains on June 6, 1934. The family history and past history were irrelevant. Catamenia was said to be regular. She had not been out of San Francisco for six months. She was almost constantly troubled by flea bites. For two days before the onset of the pains she had a generalized cutaneous rash "like hives." Her physician thought that it was urticaria, but epinephrine did not afford relief. The rash subsided, but the next day the patient had intense pains "in the muscles and joints and all over from the neck down, so she could not move." A severe frontal headache was also present. Prostration was marked. The temperature rose to 103 F. on the second day. The pains in the limbs were so marked that the physician suspected trichinosis and made a blood count. The white cells numbered 8,000, and no eosinophils were found. On the third day she was free from pain and much improved, although the temperature was 101 F. On the fifth day the severe headache returned; the temperature rose to 103.5 F., and the patient seemed so ill that she was sent to the hospital.

Physical examination showed a flushed well nourished Japanese woman complaining of severe frontal headache and cramps in the lower part of the abdomen. The conjunctivae were slightly injected. The pupils were normal. No evidence of infection was found in the nose and throat. The neck was not stiff. The heart and lungs were not remarkable. The lower portion of the abdomen was tender to pressure, but no masses or organs were palpable. Pelvic examination suggested an early stage of pregnancy with danger of abortion. The deep reflexes of the legs were not unusual. Enlarged lymph glands could be readily felt in the right post-auricular region, on both sides of the neck, in the left axilla and in both groins. During the next three days there was gradual improvement except for the onset of such severe itching of the extremities that the patient could not sleep at night and scratched her skin deeply. The temperature varied between 102 F. and 103 F. on the first two days in the hospital; it averaged about 101 F. on the third day and was normal for the first time on the fourth day of hospitalization, which was the

eighth day of the illness. There were two slight subsequent rises in the next thirty-six hours before the temperature remained normal. The pulse rate varied in proportion to the severity of the fever, and the respiratory rate was not increased. No cutaneous rash occurred during the patient's stay in the hospital. The itching persisted for about a week, and about two weeks after this illness the patient aborted at home.

The urine was normal. There was no anemia. Complete studies of the white blood cells were not carried out, but the results of the studies that were made are recorded in table 2 and in figure 2. The Wassermann reaction of the blood was negative. The sedimentation rate was 24 mm. in forty-five minutes and 25 mm. in sixty minutes. Blood cultures and agglutination tests for B. typhosus, Br. abortus and Brucella melitensis gave negative results. The cerebrospinal fluid obtained on the sixth day was normal. The Friedman test for pregnancy was positive.

The onset of a short biphasic high fever preceded by a rash, ushered in with prostrating pains, terminating with intractable itching, accompanied by glandular enlargement and leukopenia and resulting in an abortion all suggest the classic picture of dengue.

CASE 7.—A. B. C., a 35 years old garage worker, married, was interviewed six days after his illness through the courtesy of Dr. J. M. Read, who had made a tentative diagnosis of "breakbone fever" as he was familiar with the findings in the first five cases reported. The patient had been camping out at Dardanelles in Tuolumne County, Calif., and while he was riding through the brush a tick had entered the left leg. Six days later, after his return to San Francisco, he noted marked aching in the hips and "on each side of the backbone." For the next two days he had terrifically severe aching in the sacro-iliac region and in that of the hip and also in the upper portion of the legs and in the back and shoulders. He had had grip and said the present pain was far worse than anything he had experienced previously. He also had pain in the testicles "as if they were continually being squeezed." He recalled no other outstanding symptoms and had not taken his temperature. He felt much better on the fourth day and was free from pain, but he grew feverish on the fifth day and then called in Dr. Read. The temperature at that time was 103 F., and the patient was prostrated. The temperature was lower on the sixth day, and steady improvement occurred thereafter although the patient stated that his body still felt tired all over as if he had just walked many miles.

The type and distribution of the pains, particularly the testicular involvement, the division of the illness into two distinct episodes with a high fever and the lack of respiratory symptoms suggest the clinical picture of a relatively mild attack of dengue. Although the occurrence of a tick-bite fever has been reported in California, the disease is not known to occur in Tuolumne County, and it is usually associated with the typical petechial rash.

CASE 8.—J. W. C., a 26 year old physician, single, who worked in a pathologic laboratory, became ill on July 22, 1934. His past history was not unusual except for the fact that he had suffered with chronic sinusitis for years. He had not been out of San Francisco during the summer. He was troubled a good deal by flea bites. The first day of his illness he suffered from general malaise and had a slight

cough. The next day he had some aching and felt ill but kept at work. That evening the temperature was 101 F. He was prostrated for the next two days and suffered from extremely severe generalized aching from head to foot, including the limbs. The temperature reached 104 F. each day. The patient was admitted to the hospital at noon on the fourth day of the illness. Physical examination revealed no evidence of infection of the respiratory tract and showed nothing to account for the fever. The inguinal lymph glands were moderately enlarged. The next morning the temperature fell to normal and remarkable improvement seemed to have occurred. The temperature rose again that evening, and on the sixth and seventh days it varied between 100 and 104 F., returning to normal on the eighth day. During this exacerbation of the fever the spleen was readily palpable and scattered râles developed in the chest. The patient did not cough or feel particularly ill, but he suffered from such intense generalized itching that he could not sleep. The râles in the chest increased on the eighth day, and on the ninth day roentgenograms showed a small area of grayness in the middle field of the right lung despite the fact that the patient seemed quite well clinically. Two days later the râles had cleared and the roentgenogram showed that the lung was nearly normal. During the illness the pulse rate ranged from 84 to 128 and the respiratory rate from 18 to 24.

The urine and sputum were normal. Culture of the blood gave negative results. The red cells numbered 4,665,000, and the hemoglobin was 93 per cent. The total leukocyte counts fell within the normal range and are recorded in table 2.

The hospital record of this patient was made available through the courtesy of his physicians, Dr. A. Stockton and Dr. D. Hines. A diagnosis of dengue was suggested by Dr. W. Dock, who saw the patient in consultation and who was familiar with the previous reports. The clinical course of the disease is in keeping with that of the manifestations in the previous cases as it showed a self-limited fever lasting eight days with generalized aching at the onset and pronounced pruritus in the latter part of the illness. Respiratory disturbances were not noteworthy until after improvement set in. There was definite splenomegaly, and leukocytosis did not occur.

CASE 9.—A. K., a 19 year old schoolboy, was seen during his illness at the hospital through the courtesy of his physicians, Dr. E. Olsen and Dr. E. B. Shaw. His previous history was irrelevant except for the fact that he had been troubled much by flea bites shortly before his illness and there had been mosquitoes in the house, although he did not recall having been bitten. The afternoon before admission to the hospital there developed "at 4 o'clock in the afternoon" a severe frontal and occipital headache and backache; the eyes ached and were sensitive to light. The next day there was a high fever, and the patient was prostrated and seemed ill. His physician thought that the neck was slightly stiff, but he found no other abnormalities on physical examination. He suspected that the patient might have poliomyelitis and sent him to an isolation hospital for lumbar puncture and observation. The temperature on entry was 103.4 F. There was marked photophobia. The next day the aching stopped; the eyes ached less, and the temperature dropped to normal. The fever returned on the following day, the fourth day of the illness, and a faintly pink maculopapular rash developed over the chest, abdomen, back and thighs. All the subcutaneous lymph glands were noted to be enlarged, and the spleen was just palpable. The rash was more pronounced on the fifth day; on

the sixth day it disappeared, the fever ceased and the patient seemed quite well again. The course of the fever from the second day on is shown in figure 7. The pulse rate was increased in proportion to the temperature. The respiratory rate varied between 20 and 22.

Examination of the urine showed nothing unusual. The hemoglobin was 100 per cent. The white cell counts showed leukopenia. The results of the counts are shown in table 2 and in figure 2. The sedimentation rate was 20 mm. in three hours. The Wassermann reaction of the blood was negative. Agglutination tests for Brucella and Bact. tularense were negative. The cerebrospinal fluid was clear. The pressure was 75 mm. of water. The Pandy and Nonne tests were negative.

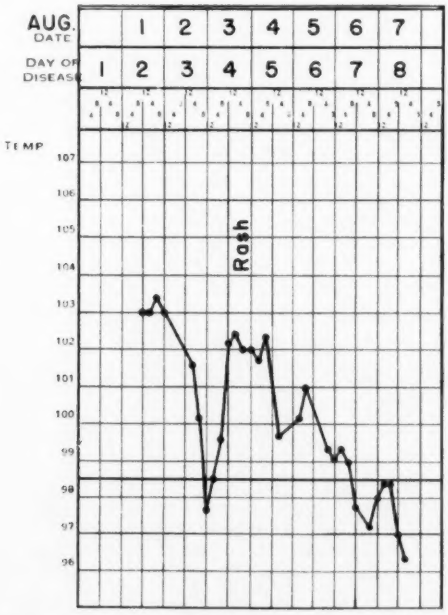

Fig. 7 (case 9).—Curve for temperature, showing the characteristic biphasic form of seven day fever.

There were 2 lymphocytes per cubic millimeter of fluid. The sugar content was normal. Cultures of the fluid were negative. A Weil-Felix agglutination test was negative.

The sudden onset of severe headache, backache and photophobia, the biphasic temperature lasting six days, the late rash, the enlargement of the lymph glands and spleen and the leukopenia in the absence of involvement of the respiratory tract make up an almost complete picture of dengue.

Case 10.—J. D. J., a 26 year old housewife, was first seen on Aug. 29, 1934. She complained of weakness, persistent vomiting and jaundice. Extensive psoriasis

had been present since childhood. She had been married three and one-half years and had three children living and well; the youngest was 3 months of age. She was a trained nurse and was known to have been anemic for four or five years, the hemoglobin content of the blood varying between 50 and 60 per cent. She had menorrhagia due to small fibroids and had been underweight since the birth of her first child. No mosquitoes were observed about her home, and she did not suffer from flea bites, although all her children were badly bitten. Her husband had been brought home from work out of town suffering from high fever, prostration and jaundice. He was up and about but was still weak and yellow when she became ill.

On August 19, ten days before she first came under medical observation, she suddenly grew sick, with high fever, aching and prostration. The temperature was 104 F. for three days, and severe headache and backache were present. The patient complained of "the worst pain in the sacro-iliac regions." The limbs ached less severely, but there were pain and stiffness in "all the joints" although no swelling was noted. There was no coryza, sore throat or cough. The patient was so ill that she did not know whether there was a rash or not or whether she had conjunctivitis. On the fourth day all the painful symptoms were relieved, and the temperature returned to normal. However, there developed persistent vomiting, anorexia, a taste in the mouth "like a bird cage" and constipation. The temperature rose again on the fifth day and varied between 101 F. and normal for the next three days. There had been only a slight rise in the afternoon for the previous two days, but on the ninth day the patient first noted a definite yellow color of the eyes and skin.

Physical examination revealed a young woman much underweight, anemic and jaundiced. The scleras were yellow. The pupils responded normally to light. The tongue was covered with a light tan coating. The teeth were in good condition, and the gums and pharynx appeared free from inflammation. The heart and lungs were not remarkable. The blood pressure was 122 systolic and 78 diastolic. Abdominal examination showed the liver to be enlarged 1 fingerbreadth below the right costal margin and exquisitely tender. The spleen was not palpable, and splenic dulness was not increased. The knee jerks and ankle jerks were lively and equal. Small glands could readily be palpated in the left cervical region; the patient had noted early in her illness that the glands were enlarged both in the axillae and in the groins. The skin showed old lesions of psoriasis. The temperature was 99 F., and the pulse rate, 80.

The urine was normal. The blood count showed 3,300,000 red cells and 60 per cent hemoglobin. Leukopenia was present, the details of which are recorded in table 2. The sedimentation rate was 9 mm. in forty minutes and 13 mm. in one hour. The icteric index was 25 units.

Six days later the patient was seen again, and there was much improvement. There had been no further vomiting and no fever. The liver was not palpable, and there was only slight tenderness at the right costal margin. The icterus had almost cleared up. The icteric index was 14 units. Ten days later the patient felt well and was no longer jaundiced, but the icteric index was 12.5 units.

Note on Illness of Patient's Husband.—It was not possible to interview this patient's husband, but she gave the following facts about his illness: On August 11 he returned home from a week's trip on a boat. He had sailed from San Francisco to Seattle and returned. Before that trip he had not been out of San Francisco for several months. The last three or four days on the boat he was acutely ill. The fever was high and there was generalized aching. He was ill at home for three or four days, and then jaundice and soreness in the right side

developed. This occurred about the eighth day of his illness and about four days before Mrs. J. D. J. became ill.

This young woman gave a clear history of high fever with headache and marked generalized aching followed by severe vomiting and jaundice. She was found to have generalized adenopathy, tenderness of the liver and leukopenia. The jaundice cleared quickly. These findings following the occurrence of a similar illness in her husband are suggestive of dengue with hepatitis and are similar to the disturbances exhibited by two of the patients in whom the disease was produced by inoculation. The illness seemed too acute and the jaundice too brief to be characteristic of the ordinary catarrhal jaundice.

COMMENT

As the findings in these ten cases are so like those seen in cases of dengue in most respects, the diagnosis of this disease must be carefully considered.

The following points are important in considering a diagnosis of dengue:

1. The clinical picture is characteristic but may be closely simulated by several other conditions. It has been adequately described by a number of authors, including Siler, Hall and Hitchens.[2] They worked in the Philippines and in 1926 published a valuable monograph. This picture may be presented most concisely by quoting from them:

> Typical cases are characterized by sudden onset with physical weakness, headache, postorbital pain and soreness, flushing of the face, suffusion of the eyes, anorexia with loss of the sense of taste, backache, pain in the bones and joints, marked prostration, mental depression, and a general feeling of wretchedness. There is a secondary or terminal eruption of a polymorphous character.

2. There is a short period of high biphasic fever averaging less than a week; the fever is not associated with leukocytosis and is usually accompanied by pronounced leukopenia.

3. The presence of such a disease in epidemic form is highly characteristic, as it affects a community more completely than nearly any other infection. Endemic cases occur in an area in which epidemics prevail and consequently are readily recognized.

4. There must be present a vector capable of transmitting the disease.

5. The disease can be experimentally produced in primates[3] by injections of whole blood or of serum even after it has been passed

2. Siler, J. F.; Hall, M. W., and Hitchens, A. P.: Dengue Fever: Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity and Prevention, Philippine J. Sc. **29**:1, 1926.

3. Simmons, J. S.: Dengue Fever, Am. J. Trop. Med. **11**:77, 1931.

through a Berkefeld filter. Direct inoculation with blood produced the disease in practically 100 per cent of nonimmune persons. The inoculation of certain races of monkeys [4] may give positive results, but no other laboratory animals are susceptible to the disease, although the virus may appear in the blood of guinea-pigs without producing any clinical manifestations.[5] All methods of culturing the virus are discredited at present.

The symptoms and signs observed in this small series of ten cases conform closely to those described in detail by the Philippine authors who emphasized that the symptomatology of dengue may be more extensive and variegated than the usual description found in textbooks suggests. This is well illustrated by the division of cases in the epidemic which prevailed in Athens, Greece, in 1928 into seven groups. Four hundred thousand cases occurred, and Bensis [6] described cases in which hyperpyrexia, rheumatic and hemorrhagic symptoms and disturbances of the gastro-intestinal tract, heart, adrenal glands and nervous system were noted. An adequate idea of the polymorphism of dengue can best be obtained by reading the original description of various widely separated epidemics.[7]

Only certain findings characteristic and distinctive of dengue which seem to have their counterpart in the manifestations observed in the local cases will be discussed. Severe pain is a dominant feature, and because of the intensity of the pain in the back and limbs the disease is widely known as break-bone fever. The pain is often most excruciating in the sacro-iliac region and may involve a certain area, such as a shin

4. Dinger, J. E., and Snijders, E. P.: Relation of Dengue to Development of Immunity Against Yellow Fever: Experimental Studies, Arch. f. Schiffs- u. Tropen.-Hyg. **35**:497, 1931.

5. Blanc, G.; Caminopetros, J., and Manoussakis, E.: Quelques recherches expérimentales sur la dengue, Bull. Soc. path. exot. **21**:525, 1928.

6. Bensis, W.: Etude clinique de la dengue, Paris méd. **2**:137, 1931.

7. (*a*) Rush, B.: Medical Inquiries and Observations: An Account of the Bilious Remitting Fever, as it Appeared in Philadelphia in the Summer and Autumn of the Year, 1780, Philadelphia, Prichard & Hall, 1789. (*b*) Dickson, S. H.: On Dengue: Its History, Pathology and Treatment, Philadelphia, Haswell, Barrington & Haswell, 1839. (*c*) Nothnagel, C. W. H.: Encyclopedia of Practical Medicine, Philadelphia, W. B. Saunders Company, 1910, vol. 10, p. 719. (*d*) Cleland, J. B.; Bradley, B., and McDonald, W.: Dengue Fever in Australia: Its History and Clinical Course, Its Experimental Transmission by Stegomyia Fasciata, and the Results of Inoculation and Other Experiments, J. Hyg. **16**:317, 1917. (*e*) King, W. W.: Epidemic of Dengue in Porto Rico, 1915, New Orleans M. & S. J. **69**:564, 1917. (*f*) Lane, F. F.: A Clinical Study of 100 Cases of Dengue at St. Thomas, V. I., U. S. Nav. M. Bull. **12**:615, 1918. (*g*) Rice, L.: A Clinical Report of the Galveston Epidemic of 1922, Am. J. Trop. Med. **3**:73, 1923. (*h*) Scott, L. C.: Dengue Fever in Louisiana, J. A. M. A. **80**:387 (Feb. 10) 1923. (*i*) Siler et al.[2] (*j*) Bensis.[6]

or a shoulder blade, with greater intensity than any other part. A headache may be the most pronounced pain and may be generalized or limited to the occipital or frontal regions or to both. Arthritis of one or more joints is occasionally the outstanding complaint. Table 1 shows that severe backache was present in 100 per cent of the local cases and pain in the limbs in 90 per cent. Severe headache was also present in 90 per cent, and stiffness of the joints was complained of in 70 per cent. The description of the symptoms in case 1 gives a graphic picture of the pain and suffering that the patient experienced; the symptoms led to the suspicion that he might be suffering from dengue. In all the cases the pain and aching were out of proportion to those which commonly accompany grip and influenza and many other febrile disturbances and were actually prostrating. This is well illustrated by the words of the Japanese patient (case 6) who "could not move from the neck down."

A number of patients have a typical appearance which in itself suggests a diagnosis of dengue but may be missed if the patient is not observed early in the illness. Although this was noted in only three of the cases in the present series, it is so striking that it deserves special attention. The deeply flushed head and neck of the patient suggest that he has just emerged from an overlong stay in a Turkish bath. The eyes are puffy and bloodshot and resemble those of a mastiff. Conjunctivitis and photophobia may be extreme and recall the appearance of many children with measles. Pain back of the eyeballs is constant, and the eyeballs are tender to pressure and are often fixed, as it causes pain to move them. Such a facies has been likened to the appearance of some one who has been on a drunken debauch. An unusual disturbance in vision for color may occur, which in the absence of poisoning from santonin and a few other drugs has apparently been described only in cases of dengue. The patient sees flashes of yellow light which appear and disappear rapidly. Such a visual phenomenon was disturbing to I. A. (case 1). The possible significance of this xanthopsia was lost until it was discovered that many of the patients with dengue studied in the Philippines had the same symptoms.

Another bizarre disturbance of sensation is the loss or the perversion of the sense of taste. This is a well recognized symptom in cases of dengue and is distinct from the loss of appetite which occurs commonly in attacks of most types of fever. It was present in four of the first five local cases and in case 10. Taste was completely lost in two cases, and in the other three the patients stated that all food tasted the same. To two of these patients everything tasted dead or putrid, and to the other even sugar tasted sour.

Gastro-intestinal disturbances are a striking feature of some epidemics of dengue and at times have led to unnecessary laparotomy.[6]

They have been of minor incidence in other outbreaks.[8] The tongue usually shows a thick creamy coating. Vomiting and pain in the upper part of the abdomen may be marked. The vomitus is clear or bile-stained but is not "black" as in cases of yellow fever. The gastric pains and distress are said to be due to an "enanthema" of the gastric mucosa comparable to the rash on the skin.[6] Constipation is common, and in some cases diarrhea is present and may be severe. Gastro-intestinal disturbances were conspicuous in only two of the cases observed (cases 1 and 10).

Symptoms of involvement of the respiratory tract are noteworthy only on account of their frequent absence. Sore throat, bronchitis or complicating pneumonia occurs rarely in cases of dengue, although marked reddening of the pharynx is not uncommon. A condition called "pleurodynia"[9] is possibly a form of dengue, and pains in the chest and pleurisy are a feature of that disease. However, râles in the chest with slight cough were present in four of the first five local cases and in case 8. These signs appeared late in the disease and were usually most marked when the fever had subsided and much improvement had occurred. The râles were coarse and moist, were heard at the base of one or both lungs, shifted frequently and were unaccompanied by any other unusual signs except perhaps the slight dulness noted in case 8. In this case a definite shadow in the roentgenogram of the right pulmonary field appeared after the fever subsided and cleared quickly, showing that more than a bronchitis was present. Unfortunately no roentgenograms were made in the other cases.

The cutaneous manifestations of rash and severe itching are of great diagnostic value. The rash has been well described by Rice [7j] and occurs at two stages of the infection. There is an initial evanescent mottling, which is often missed, so that its frequency is difficult to determine and its importance is slight. The more characteristic cutaneous eruption usually occurs during the second stage of the fever or appears terminally and is responsible for the names "spotted fever" and "giraffe fever." It may assume a variety of forms and is often macular or scarlatiniform. In some epidemics it is present in 80 per cent of the cases.[10] Osler stated that it is present in only 40 per cent of the cases.[11] Rush,[7a] in the first description of dengue in the United States, written in 1789,

8. Siler et al.[2] Lane.[7f]

9. Dabney, W. C.: Account of an Epidemic Resembling Dengue Which Occurred in and Around Charlottesville and the University of Virginia in June 1888, Am. J. M. Sc. **96**:488, 1888. Torrey, R. G.: Epidemic Diaphragmatic Pleurodynia or "Devil's Grip," Am. J. M. Sc. **168**:564, 1924.

10. Siler et al.[2] King.[7e]

11. McCrea, T., in Osler, W.: Modern Medicine, Its Theory and Practice, Philadelphia, Lea & Febiger, 1925, vol. 2, p. 1420.

hardly mentioned it, but Dickson [7b] in 1839 considered it an essential part of the symptomatology. Table 1 shows that an initial rash was noted in only one of the seven cases observed and that a late rash appearing in a late stage was present in 30 per cent of the cases in this series.

Pruritus may be intense and often precedes the appearance of the secondary rash, and in a number of cases it is apparently substituted for the latter as no discoloration of the skin occurs. When this severe itching is present it is an outstandingly distressing manifestation and is highly suggestive of dengue, as it has not been described as a feature of other short febrile disorders. It was present in cases 1, 3, 4 and 8. In three of these cases scratching could not be controlled for two or three days.

Two of eight male patients (cases 1 and 7) complained of pain and some tenderness in the testicles, a symptom which has been said to be common in cases of dengue.[2] It may be in keeping with general aching in other parts of the body, but Nicolas [12] has reported a group of five cases with definite orchitis. A generalized moderate enlargement of the lymph glands is frequently observed and was noted in three of the cases produced by inoculation and in cases 6, 9 and 10 of this series. It may have been present in case 7. In case 8 the inguinal glands were large, but the patient thought they had been large for years. The latter patient and A. K. (case 9) had enlargement of the spleen, a disturbance which also occurs in dengue.[7d]

The curve for temperature is not diagnostic of dengue but in certain respects is highly suggestive. Ordinarily there is a rapid rise in temperature followed by a short course of fever for a few days, the temperature often dropping to normal or subnormal at about the middle of the febrile period, and a more or less abrupt termination. The names "three day fever," "five day fever" and "seven day fever" best illustrate the brevity of the pyrexia. The characteristic diphasic or saddleback fever is often lacking in epidemic cases and is more frequently encountered in cases produced by inoculation.[13] The temperature commonly reaches 102 or 103 F. and may reach 105 F. or over.[14] There may be slight rises after the acute illness has terminated. Various forms of curves for temperature have been described by Rice [7g] in his report on the epidemic which occurred in Texas in 1922.

The curves for temperature for cases 1, 2 and 9, (figs. 1, 3 and 7) may be taken as excellent examples of the course of fever in dengue, as

12. Nicolas, C.: Six cas d'orchite ou ovarite, complications de la dengue, Bull. Soc. path. exot. **20**:402, 1927.

13. Siler et al.[2] Simmons.[3]

14. Watson, M.: A Case of Dengue Fever with Hyperpyrexia, J. Trop. Med. **36**:157, 1933.

they conform so closely to the usual description and vary from those for other forms of fever usually encountered. Two paroxysms of fever could be readily recognized in 60 per cent of the cases, although the interval of low temperature was relatively short, lasting for a number of hours rather than for days. The curve in case 5 (fig. 6), one of the cases produced by inoculation, was the only one which is unlike the usual picture, but the complicating factor of hepatitis may be responsible. The temperature reached 103 F or over in all ten cases, and the duration varied between six and nine days, as shown in table 1. It should be emphasized that a short attack of high fever with a low white cell count should, in the absence of any obvious cause, suggest the possibility of dengue and the necessity of evaluating all the clinical findings with this diagnosis in mind.

The pulse rate in dengue may be rapid [11] but has often been described as remarkably slow.[6] In the cases reported here it varied in proportion to the intensity of the fever, and no bradycardia was evident.

The blood picture in dengue has been carefully studied by a number of observers.[15] The number of red cells and the hemoglobin content are not affected. Moderate leukopenia, the count averaging from 3,500 to 5,000 white cells, is present in about three fourths of the cases and becomes most pronounced toward the termination of the illness. The leukocyte count may be unaltered, and at times there is slight leukocytosis in early stages of the disease.[16] When there is leukopenia the diminution of cells affects the polymorphonuclear leukocytes, producing a relative increase in the proportion of the mononuclear cells. The young forms of polymorphonuclears are increased in the early stages of the infection, producing a characteristic shift to the left in the Schilling count, and Catsaras [17] has reported marked degenerative changes in the older cells; he expressed the belief that this is direct evidence of a toxic action of the virus on the leukocytes. Joannides [15b] agreed with this theory and also noted similar changes in the large mononuclear cells, which may be increased in number.

Of the present series of ten cases, blood counts were made in nine (table 2 and fig. 2). No definite conclusions can be drawn from an analysis of such a small series, particularly as four of the patients (cases 2, 3, 5 and 8) suffered from complications which may well have

15. (*a*) Simmons, J. S.; St. John, J. H., and Reynolds, F. H. K.: Numerical and Morphological Alterations of Leukocytes, Philippine J. Sc. **44**:128, 1931. (*b*) Joannidès, G. S.: Blood in Dengue: Morphological Examination, Arch. Inst. Pasteur hellén **2**:295, 1930. (*c*) Siler et al.[2] (*d*) Dinger and Snijders.[4]

16. Siler et al.[2] Dinger and Snijders.[4]

17. Catsaras, J.: Pathologish- anatomische Beobachtungen zum Dengue Fieber, Arch. f. Schiffs- u. Tropen-Hyg. **35**:278, 1931.

altered the white blood cell count. None of the patients became anemic. Table 2 shows that in repeated counts throughout the illness in cases 4, 6 and 9, in which there were no complications, pronounced leukopenia developed. In each a relative increase in the number of monocytes occurred as the diminution in the total number of white cells progressed. In two of these cases Schilling counts were made, and in each of the counts the percentage of early forms of polymorphonuclear neutrophils predominated over that of mature forms. The patients, then, showed the characteristic changes typical of dengue. In case 1 only two cell counts were made, and these were made on the third and fourth days of the illness. The total counts were in the normal range, but there was a marked shift to the left in the Schilling count. Regarding the cases in which complications occurred, the extreme leukocytosis in the first two patients with jaundice will be commented on further later. However, the first of these patients (case 3) had the increase in leukocytes from the third day on, together with a marked excess of neutrophils and many banded forms, while the second (case 5) had a normal number of leukocytes on the fourth and fifth days, with many immature forms, and then from the seventh day on had leukocytosis characterized by relative lymphocytosis and a Schilling count close to normal. It is difficult to explain why in one of these patients there developed a blood picture compatible with any acute infectious process and in the other there developed an extraordinary lymphocytosis. Perhaps the bronchopneumonia noted at autopsy affected the white cell count in case 3. Although the third jaundiced patient (case 10) did not come under observation until the tenth day of her illness, she showed definite leukopenia with a diminution in the number of neutrophils and a shift to the left.

The lymphocytosis that appeared in case 2 when encephalitis developed was much like that in the second case of jaundice and may represent the true reaction to the virus when it produces complications. In case 8 the blood counts on the fourth and seventh days showed a total number of leukocytes within the normal range and an increase in neutrophils, with a high percentage of banded forms. An infection of the respiratory tract which developed in a late stage of the disease was evident in this patient.

The production of the clinical picture of the inoculation type of dengue in a human volunteer by injection of blood from I. A. (case 1) may be considered the most conclusive diagnostic evidence obtained that the original patient was infected with that disease. The further transmission of the fever to other patients serves to strengthen this conclusion. Similar experiments have been carried out in widely separated medical centers, such as Manila, P. I.,[13] Sydney, Australia,[7d] Amster-

dam, Netherlands,[4] London, England,[18] Athens, Greece [19] and Galveston, Texas,[20] and the same results have always been obtained. No unusual complications and no fatalities have been reported. As little as 0.00005 cc. of serum from patients with dengue injected subcutaneously [21] has produced infection, and the amount of infective material used does not seem to alter materially the course of the disease produced. The blood is infective only during the first three or four days of the illness, and the virus remains viable when kept as long as ninety-nine hours at icebox temperature.[7d] One observer [19] has stated that the cerebrospinal fluid also contains the virus during this period, but no careful study of the spinal fluid has been reported. The virus is not present in the urine, stool or sputum. The period of incubation following inoculation may be from one to nine days but is between four and five days on the average. Table 1 shows that in cases 2 to 5 of this series the period of incubation was four days in three cases and two and one-half days in the fourth case. The average length of the illness is shown to be slightly less than eight days, which is a little longer than the average for most similar series but is in keeping with that in the six endemic cases reported.

The results of inoculating monkeys with dengue have been carefully studied.[22] It need only be stated here that certain races seem to be immune and that in others the degree of infectivity is not high. Some monkeys are infected, and although they show no clinical signs of the disease, not even fever, they usually manifest definite leukopenia. Unfortunately the two monkeys which received injections of blood from L. H. (case 5) were not followed with this in mind, and clinically negative results in only two animals are of no positive value.

The fact that the results of injections of two serums into volunteers were negative may be explained in two ways: Although serum was drawn from the same whole blood which was proved to contain the virus, the longer periods of five and seven days during which it was kept in the icebox may have made it innocuous. It is also possible that the two volunteers were immune. There was no history to suggest this, but it should be borne in mind that they were both suffering from chronic encephalitis, which is due to a filtrable virus. The negative

18. Findlay, G. M.: The Relation Between Dengue and Rift Valley Fever, Tr. Roy. Soc. Trop. Med. & Hyg. **26**:157, 1932.

19. Manoussakis, E.: Recherches étiologiques sur la dengue, Bull. Soc. path. exot. **21**:200, 1928.

20. Chandler, A. C., and Rice, L.: Observations on the Etiology of Dengue Fever, Am. J. Trop. Med. **3**:233, 1923.

21. Koizumi, T.; Yamaguchi, K., and Tonomura, K.: A Study of Dengue Fever, Trop. Dis. Bull. **12**:77, 1918.

22. Siler et al.[2] Simmons.[3] Dinger and Snijders.[4] Blanc et al.[5] Findlay.[18]

result in a volunteer with chronic arthritis who received an injection of cerebrospinal fluid from A. G. P. (case 2) is not surprising as the fluid was obtained ten days after the acute illness was over.

COMPLICATIONS

Complications and sequelae of dengue are said to be singularly uncommon. In general this is true, but a variety of forms may occur, as may be gathered from Bensis'[6] experiences in the extensive epidemic which prevailed in Athens, Greece. It is remarkable that four of the first five patients for whom data are given in table 1, all of whom suffered from an identical infection, had complications. The albuminuria shown by I. A. (case 1) was marked. The tremendous number of casts observed has never been encountered by me in any other febrile condition and is comparable to the urinary sediment described as occurring in yellow fever. Such a degree of albuminuria is rare in dengue but has been recorded.[23]

Complications of dengue affecting the central nervous system have been noted, and they vary widely in their manifestations,[24] but clinical signs and changes in the cerebrospinal fluid typical of encephalitis such as those which appeared in the postfebrile stage in case 2 have not been described although Ghiannoulatos [24a] mentioned that encephalitis occurred in association with dengue in the epidemic in Athens, Greece. However, encephalitis is a well recognized, even if rare, complication of diseases caused by a filtrable virus, such as measles, mumps, smallpox, vaccinia, rabies and other conditions,[25] and a neurotropic virus of yellow fever has been isolated.[26] The temporary change in character, the extreme drowsiness, the dull headache with slight fever and the leukocytosis are strikingly similar to forms of epidemic encephalitis encountered over a decade ago. Lumbar puncture showed that the fluid was under increased pressure and that there was an increase in the protein content and in the number of cells. Inability to demonstrate the presence of an infective agent in the fluid by inoculation into human subjects is in keeping with the results

23. (*a*) Avaritsiotis, E.: Sur le neurotropisme de la dengue, Ann. de méd. **30**: 5, 1931. (*b*) Bensis.[6]

24. (*a*) Ghiannoulatos, G. P.: Aperçu clinique sur les séquelles nerveuses et psychiques de la dengue (Un cas de pseudo-tabes), Rev. neurol. **1**:599, 1931. (*b*) Richardson, S.: Ocular Symptoms and Complications, Tr. Am. Ophth. Soc. **31**: 450, 1933. (*c*) Avaritsiotis.[23a]

25. Rivers, T. M.: Relation of Filtrable Viruses to Diseases of the Nervous System, Infections of the Central Nervous System, A. Research Nerv. & Ment. Dis. Proc. **12**:49, 1932.

26. Davis, N. C.; Lloyd, W., and Frobischer, M.: Transmission of Neurotropic Yellow Fever Virus by Stegomyia Mosquitoes, J. Exper. Med. **56**:853, 1932. Rouband, E., and Stefanopoulo, G.: Transmission of Neurotropic Yellow Fever Virus by Stegomyia Mosquitoes, Bull. Soc. path. exot. **26**:305, 1933.

of similar experiments on monkeys inoculated with cerebrospinal fluid from subjects with other forms of secondary encephalitis. Ordinarily, in the early stage of dengue, when the virus is said to be present in the spinal fluid, no pleocytosis or other changes occur, and the negative results of lumbar puncture in cases 6 and 9 are in keeping with this. Catsaras [17] reported the observations made at autopsy on a patient with dengue associated with acute encephalitis.

Jaundice is said to be an uncommon complication of dengue but is well recognized. Two reports suggest that it may be frequently encountered at times. In 1923 about 29,000 cases of dengue were reported in Louisiana.[7h] A questionnaire concerning its manifestations was sent out to all the physicians. Twenty-eight per cent of those who answered it had noted jaundice in their cases. Also in 1928 Nicolas in Northern Africa reported a small group of twenty cases of dengue, in eight of which jaundice was present.[27] As jaundice was noted in three cases in San Francisco (cases 3, 5 and 10) and as in each of the two produced by inoculation it appeared on the sixth day of the disease and in each of these was accompanied by a marked leukocytosis, its occurrence could hardly be a coincidence. Figure 4 also shows the degree of icterus in the three cases to be identical. As J. B. (case 3) had previously been slightly jaundiced with an attack of disease of the gallbladder it was at first thought that the reappearance of jaundice was on the same basis. The remarkable picture of hepatic necrosis noted at autopsy could hardly be unrelated to his infection. It may have occurred because the liver had been previously damaged. No report of a postmortem examination of a patient with dengue associated with jaundice can be found in the literature for comparison. This suggests that cases of "catarrhal jaundice" and acute hepatitis of unknown etiology may be due to a similar type of infection. The second patient was disturbed little by the icterus, although it was accompanied by prolonged fever and leukocytosis. The third patient was incapacitated for only a few days. No records of blood counts of patients with dengue associated with jaundice can be found in the literature to compare with the high white cell count observed in two of these cases.

DIFFERENTIAL DIAGNOSIS

The clinical findings and complications occurring in this small group of cases in San Francisco do not seem compatible with any of the conditions ordinarily encountered and are so like the picture of dengue that no differentiation from it is possible. The differential diagnosis in these cases is the same as that for sporadic cases of dengue appearing

27. Nicolas, C.: A propos d'une épidémie de dengue compliquée d'ictère: La dengue serait-elle une fièvre amarylle atténuée? Bull. Soc. path. exot. **21**:748, 1928.

in this locality and offers a problem far different from that which is encountered when cases occur in the tropics, in the Orient or elsewhere where the fever is common. Inoculation experiments as an aid to diagnosis are rarely feasible, so that dengue must be differentiated from a considerable number of other diseases on clinical grounds alone, and the diagnosis can usually only be presumed, and then only on the basis of exclusion of other similar conditions.

Influenza is similar in many respects. However, its usual absence in summer, when dengue occurs, the constancy of symptoms of involvement of the upper portion of the respiratory tract, the absence of generalized glandular enlargement and of rash and the more irregular course of the fever should differentiate it from dengue. Reproduction of the disorder by injections of blood into monkeys have not produced clearcut results,[28] and similar experiments in man have not been recorded. Severe measles in an adult may be readily confused with dengue. The presence of an epidemic, the onset with symptoms of involvement of the upper portion of the respiratory tract, the presence of Koplik spots on the buccal mucous membranes and the more extensive rash should distinguish the majority of cases, although both conditions are due to infection with a filtrable virus and measles may also be transmitted by inoculation into human subjects.[29] Rubella is said to occur in a severe form[30] with headache, conjunctivitis, photophobia, prostration and high fever and with a rash appearing several days after the onset. It was considered a possible diagnosis in case 9.

Epidemic pleurodynia has frequently been reported on the Atlantic seaboard of the United States[31] and has been compared to dengue.[31a] It is similar to that disease but is characterized by the outstanding complaint of pain over the lower ribs and upper portion of the abdomen and the rare presence of a friction rub. The leukocyte count may be slightly increased, or it may be low. The mode of transmission is unknown, and mosquitoes have not been proved to be the vector. It may well be a modified form of dengue.

Typhoid as a differential diagnosis may offer considerable difficulty at first. The gradual increase in temperature with the prolonged course of the fever, the absence of conjunctivitis and of pains in the joints and limbs, the dissimilarity of the rash and, above all, blood cultures positive

28. Falk, I. S.; Harrison, R. W.; McKinney, R. A., and Stuppy, G. W.: Experiments on the Etiology of the Influenza Epidemic of 1928-1929, Monographic Series, no. 11, Baltimore, American Journal of Hygiene, 1931.

29. Degkwitz, R.: The Etiology of Measles, J. Infect. Dis. **41**:304, 1927.

30. Schamberg, J. F., and Kolmer, J. A.: Acute Infectious Diseases, ed. 2, Philadelphia, Lea & Febiger, 1928, p. 567.

31. (*a*) Paynes, G. C.: Epidemic Transient Diaphragmatic Spasm, J. A. M. A. **81**:746 (Sept. 1) 1923. (*b*) Footnote 8.

for B. typhosus should make the differentiation easy when the patient is under a prolonged period of observation. In cases 1 and 6 the condition was tentatively diagnosed as typhoid. Infections with B. abortus may temporarily simulate dengue, but the longer course of the disease associated with positive results of blood culture and agglutination tests will establish the diagnosis. Relapsing fever at onset may give symptoms identical with those of dengue. However, the leukocytosis, the presence of spirochetes in the blood and the reproduction of the infection in mice will serve to distinguish the two. It is of interest that in cases 1 and 7 the patients were bitten by ticks; this suggests the possibility of an infection not only with spirochetes but also with the rickettsia of Rocky Mountain spotted fever. Ticks with this infection are present in Northern California,[32] and all the characteristic clinical features of dengue occur in tick fever. The longer course, the hemorrhagic tendency of the rash, the slight leukocytosis with mononucleosis and the fact that the disease is readily reproduced in guinea-pigs distinguish tick fever from dengue. Typhus should be recognized on similar clinical grounds and by a positive Weil-Felix reaction. It has been reported to occur in California [33] in the mild form of Brill's disease and the Mexican tabardillo fever.

The severe headache at onset centering in the occiput and producing pain on flexing the head, the ocular signs and the fever may suggest some form of meningitis, encephalitis or even an early stage of poliomyelitis. The possibility of a meningitis was seriously considered on the sixth day in case 1, and that of poliomyelitis, on the second day in case 9. The onset of smallpox is not unlike the manifestations in dengue.

Ordinarily the natural evolution of most of the diseases mentioned will make their differentiation clear, but it may be impossible to eliminate influenza and pleurodynia and difficult to rule out severe forms of measles and rubella.

There are a large group of fevers apparently due to a filtrable virus which are at present unknown in California. Not only do they offer perplexing problems in diagnosis in the areas in which they are recognized, but the close similarity of symptomatology illustrates how difficult it is to separate clearly many of the disorders supposedly due to this type of infection. The possibility of the few cases described in Northern California belonging to this group rather than being instances of dengue itself cannot be overlooked, and a comparison of dengue with

32. Kelly, F. L.: Rocky Mountain Spotted Fever: Its Prevalence and Distribution in Modoc and Lassen Counties, California; Preliminary Report, California State J. Med. **14**:407, 1016.

33. Cumming, J. G., and Senftner, H. F.: The Prevention of Endemic Typhus in California, J. A. M. A. **69**:98 (July 14) 1917.

other clinical entities which have been confused with it will emphasize on what uncertain criteria the differential diagnosis of the whole group depends. The relationship of dengue to yellow fever is well recognized,[34] and mild cases of the latter cannot be distinguished from severe cases of the former disease. As a rule, jaundice, albuminuria and "black vomitus" together with a high mortality rate are characteristic of yellow fever, yet the same symptoms may occur in dengue. This is noteworthy in view of the fact that of the five cases of infection with the same strain of virus in this series, severe vomiting and albuminuria were present in one and jaundice in two. Both diseases occur in epidemics spread by the same kind of mosquito. An even closer relationship is shown by the fact that many monkeys inoculated with dengue acquire immunity to yellow fever.[4] However, nearly all Macacus rhesus monkeys inoculated with the virus of yellow fever die while monkeys of the same race inoculated with the virus of dengue rarely succumb. Dinger, Schuffner, Snijders and Swellengrebel [35] give an enlightening discussion on the similarity of the two disorders.

A number of fevers which have been designated as "pseudodengue" or "dengue-like" have been described in different parts of the world. The seven day fever of Rogers and the five day fever of van der Scheer are now definitely thought to be identical with dengue.[4] Papataci or sand-fly fever in Africa as described by Manson [36] is in no way different from dengue except that it is transmitted by a phlebotome and that a rash is not a feature. Also, a sand-fly fever is endemic in the region near Peiping, China; that disease runs a short uninterrupted course and has not been described in the literature.[37] The red fever occurring in the Belgian Congo may be a mild form of dengue.[38] The African Rift Valley fever, while clinically like dengue, is apparently due to a different virus. Monkeys immune to the virus of dengue are not immune to that of Rift Valley fever, and monkeys immunized against Rift Valley fever are susceptible to dengue.[18]

TRANSMISSION OF THE DISEASE

Dengue is transmitted by the bite of a mosquito. No other way of contracting the disease is recognized, and the only mosquito known

34. Dinger and Snijders.[4] Bensis.[6] Nicolas.[27]

35. Dinger, J. E.; Schuffner, W. P.; Snijders, E. P., and Swellengrebel, N. H.: Untersuchungen über Gelbfieber in den Niederlanden, Zentralbl. f. Bakt. (Abt. 1) **118**:6, 1930.

36. Manson, P.: Tropical Diseases, edited by P. H. Manson-Bahr, ed. 9, New York, William Wood & Company, 1929, p. 210.

37. Meleney, H. E.: Personal communication to the author.

38. Pieraerts, G.: Red Fever of Congo May Be Dengue, Ann. Soc. belge de méd. trop. **11**:321, 1931.

to carry the virus is Aedes Aegypti,[39] as no other forms of this insect have ever been convicted except Aedes albopictus [40] in the Philippine Islands. Professor W. B. Herms, head of the division of entomology and parasitology at the University of California, stated that Aedes Aegypti does not occur in California although Aedes varipalpus, which closely resembles it, is endemic.[41] Under these circumstances the appearance of these cases of dengue-like fever in San Francisco presupposes either that mosquitoes are now present which may transmit it or that some other vector or method of transmission is possible. During July 1934 the San Francisco Board of Health waged a campaign to clean up mosquitoes in the city as many had made their appearance during the summer. Several were killed in the home of A. K. (case 9), not far from the home of Mrs. J. D. J. (case 10). The presence of Aedes Aegypti has not been reported to date. The presence of these mosquitoes cannot be disregarded as offering a possible clue to the source of infection in San Francisco, and in two of the six endemic cases the patients evidently contracted the illness outside the city in areas well known to be infected with mosquitoes. Some interesting articles have appeared which stress the possibility of spreading mosquito-borne diseases by means of travel by air.[42] In this way infected insects can be carried long distances from endemic areas in a short time. De Vilbiss, in an article entitled "Wings of Death," [43] has described the precautions taken by the United States Public Health Service to prevent such an occurrence. Only a long series of carefully controlled experiments or the appearance of an epidemic of dengue can settle the point as to whether or not infected mosquitoes are present in San Francisco.

As it has been pointed out that yellow fever, which has always been thought to be transmitted by mosquitoes alone, has been transmitted by ticks in Brazil,[44] and as two of the patients of this series were bitten by ticks shortly before the onset of the fever, the possibility of this vector's being the infecting agent must be considered. However, as none of the other patients had been outside of San Francisco shortly before becoming ill, and as ticks do not naturally occur in the city, it is hard to see

39. Snijders, E. P.; Dinger, E. J., and Schuffner, W. P.: On the Transmission of Dengue in Sumatra, Am. J. Trop. Med. **11**:171, 1931. Siler et al.[2] Simmons.[3]

40. Simmons, J. S.; St. John, J. H., and Reynolds, F. H. K.: Dengue Fever Transmitted by Aedes Albopictus Skuse, Am. J. Trop. Med. **10**:17, 1930.

41. Herms, W. B.: Personal communication to the author.

42. Cullen, J. P.: Dengue Fever, J. Trop. Med. **35**:289, 1932. Legendre, J.: Transmission of Dengue by Land and Sea Routes, Presse méd. **41**:1261, 1933.

43. De Vilbiss, L. A.: Wings of Death (Spread of Mosquitoes by Airplane), Hygeia **11**:902 (Oct.) 1933.

44. de Beaurepaire Aragao, H.: Transmission de la fièvre jaune par les tiques, Compt. rend. Soc. de biol. **114**:137, 1933.

how these patients could have been infected in that manner, unless the disease was acquired through contact with dogs harboring the parasites.

Sand-fly fever occurs in such widely separated areas as Peiping, China, and Northern Africa,[45] and the disease clinically is so much like dengue [46] that a phlebotome may be considered as a vector. There is no evidence that this method of transmission is possible in Northern California. The majority of the patients had suffered from flea bites, but fleas are so common in San Francisco that no real significance can be attached to this. However, if fleas can transmit plague and typhus they may carry other types of infection. There is nothing in the history of the cases to suggest that the louse was a vector.

CONCLUSIONS

Six cases of high, usually biphasic, fever averaging a week in duration and not accompanied by symptoms of involvement of the upper portion of the respiratory tract or leukocytosis were observed in San Francisco during the summer of 1934. They appear to represent a disease entity new in Northern California. The clinical findings in these six cases and in four other cases produced by inoculation with whole blood are practically identical with those of dengue. The incidence of complications was higher than is usual in dengue, but their nature is the same. This may be explained on the ground that the local population is less resistant to this type of infection.

However, as dengue commonly makes its appearance in a new field in the form of a widespread epidemic and as the only known vector is the mosquito Aedes Aegypti, which has never been observed in California, the disease in these cases cannot positively be diagnosed as dengue. Also, it has not been shown that the infective agent in these cases was truly a filtrable virus, and it has not been possible to show whether an immunity to dengue developed after the attack. Under these circumstances it seems wisest at present to classify this type of febrile disorder as "dengue-like," although all the clinical evidence points toward its being dengue. It is hoped that if this fever recurs next summer its exact status may be accurately determined.

45. Manson-Bahr.[36] Meleney.[37]

46. Megaw, J. W. D.: Dengue-Sand-Fly Fever Problem, Indian M. Gaz. **58**: 401, 1923.

HYPERGLYCEMIA AND GLYCOSURIA ASSOCIATED WITH DISEASE OF THE BILIARY TRACT

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The intimate relationship of disease of the biliary tract to pancreatitis and its significance as an etiologic factor in the production of glycosuria and diabetes mellitus are generally recognized. Joslin [1] stated that cholelithiasis is one of the important etiologic factors in cases of diabetes of adults. He emphasized the importance of eradicating disease of the gallbladder in this type of diabetes and cited several cases that demonstrated the favorable influence of this procedure on sugar tolerance.

Cammidge [2] in a letter to the editor of the *Lancet* commented:

> It has long been recognized that glycosuria is a relatively uncommon result of the chronic interstitial pancreatitis associated with gall-stones, and that when it does occur it is of a mild type. But the disease is usually progressive and, although operative interference may bring about an improvement in the patient's carbohydrate tolerance, it is only temporary and frank diabetes ultimately results.

Smithies,[3] in a commentary on a paper by Barber, stated:

> So-called diabetes with gall tract disease is not a true diabetes. Glycosuria appears in from three to six per cent of these patients. The glycosuria results from indirect interference with island function consequent upon pancreatitis, and from faulty glycogen storage as a result of hepatitis. Treatment of the biliary tract diseases by non-surgical drainage or in selected instances by surgery markedly affects the glycosuria.

Lichty and Woods [4] in 1925 in an analysis of 23,464 patients found 1,474 cases of disease of the gallbladder and biliary tract, 455 cases of glycosuria and 25 cases of disease of the biliary tract with glycosuria. They reported 3 cases of diabetes mellitus apparently cured by operation on the gallbladder.

From the surgical wards of the Mount Sinai Hospital.

1. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928.
2. Cammidge, P. J.: Lancet **1**:846, 1927.
3. Smithies, F., in discussion on Barber, W. H.: Cholecystitis and Its Relation to Pancreatitis, J. A. M. A. **87**:1635 (Nov. 13) 1926.
4. Lichty, J. A., and Woods, J.: Am. J. M. Sc. **167**:1, 1924.

As long ago as 1907 Hochhaus [5] reported 2 cases of cholelithiasis with an increased severity of the associated diabetes during the acute attack. The subsidence of disease of the gallbladder was accompanied by a marked improvement in the sugar tolerance.

Rabinowitch and Bazin [6] reported several cases of disease of the gallbladder complicated by hyperglycemia. They published the dextrose tolerance curves for these patients before and after surgical procedure. The protocols presented are incomplete, but there is no doubt that in some of their patients there was a restoration of normal tolerance for dextrose. The authors' evidence for attributing the impaired tolerance for dextrose to chronic pancreatitis seems inadequate. Eustis [7] stated: "It is well known that after diabetes is established there is no cure and efforts are only palliative." He reported a series of 36 cases of so-called alimentary glycosuria. In 15 of these, or 41.6 per cent, there was definite disease of the gallbladder, and in 6 of the latter group true diabetes with hyperglycemia developed. Silverman,[8] in commenting on Eustis' observation, reported 30 cases of chronic pancreatitis secondary to disease of the gallbladder. He did not find diabetes in any patient of this series.

Kohn [9] mentioned the cases of 3 patients in whom diabetes developed while the patients were being treated for disease of the gallbladder. Two patients showed considerable improvement in their carbohydrate tolerance following operation. The third improved after duodenobiliary drainage.

Shapland [10] reported a case of diabetes complicated by gallstones. The diabetic symptoms preceded the symptoms of cholelithiasis by at least two years. The duration of the diabetes was eight years. Surgical removal of the gallbladder resulted in improved tolerance for carbohydrates.

Baker and Rynearson [11] have recently reported improvement in the diabetic status following cholecystectomy in 2 patients, in 1 of whom definite hepatitis was noted on gross examination.

Himsworth [12] reported the case of a patient under care for a condition of the liver requiring surgical intervention. There was no previous history of diabetes, but on admission to the hospital a trace of sugar

5. Hochhaus: Deutsche med. Wchnschr. **33**:1677 (Oct. 10) 1907.
6. Rabinowitch, I. M., and Bazin, A. T.: Ann. Surg. **94**:354, 1931.
7. Eustis, A.: New Orleans M. & S. J. **75**:449, 1923.
8. Silverman, D. N.: New Orleans M. & S. J. **75**:592, 1923.
9. Kohn, L. W.: New York State J. Med. **26**:182, 1926.
10. Shapland, C. D.: Lancet **1**:758, 1927.
11. Baker, T. W., and Rynearson, E. H.: Proc. Staff Meet., Mayo Clin. **9**:81, 1934.
12. Himsworth, H. P.: Clin. Sc. **1**:1, 1933.

was found in the urine. Under observation this condition became worse, until 140 units of insulin was given without controlling the glycosuria and ketonuria. Autopsy revealed the bile ducts throughout the liver to be blocked with gallstones and the liver grossly damaged. The pancreas was normal.

The association of the disease of the biliary tract and diabetes has been definitely established, but the nature of the underlying disturbance of carbohydrate metabolism remains obscure. Ever since Opie [13] demonstrated the relationship of cholelithiasis to disease of the pancreas it has been assumed that the glycosuria is a manifestation of the associated pancreatitis. Warren [14] pointed out the tendency to relate complacently almost any type of pancreatic lesion to diabetes without much regard to changes seen in the pancreas of nondiabetic persons. Any lesion found in the pancreas of a diabetic person which involves either the island tissue or the acinar tissue, or both, can be duplicated in the pancreas of a nondiabetic person. The acceptance of the interstitial pancreatitis of disease of the gallbladder as a complete explanation of the disturbance of carbohydrate metabolism fails to consider the much greater frequency with which this same pathologic condition is not associated with either hyperglycemia or glycosuria.

The evidence that the improvement in the diabetic status following biliary drainage is due to the removal of a focus of infection is not entirely convincing. There was no definite evidence of infection in several of the cases reported. Furthermore, there is no such striking improvement following the removal of a similar focus elsewhere in the body.

The possible hepatic origin of glycosuria and hyperglycemia has been suggested, a theory supported by the extensive damage to the liver often encountered in cases of disease of the biliary tract.

REPORT OF CASES

CASE 1.—A man aged 63 years was admitted to the hospital on Feb. 21, 1934. Eight months before he had had an appendectomy, at which time glycosuria was not noted. For one month before admission to the hospital there had been intermittent nonradiating colicky pains in the epigastrium. There had been an acholic stool five days, and another one day, before admission to the hospital. When the patient was first seen there was slight jaundice. The edge of the liver was palpable 3 cm. below the costal margin. Definite tenderness was elicited in the right upper quadrant of the abdomen. The systolic blood pressure was 130 mm. of mercury and the diastolic 78 mm. Physical examination otherwise gave essentially negative results. The stools were light gray. The urine contained 2 per cent sugar but no acetone. The concentration of cholesterol was 250 mg. and that

13. Opie, E. J.: Diseases of the Pancreas, Philadelphia, Lea & Febiger, 1926.
14. Warren, Shields: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930.

of the sugar, 185 mg., per hundred cubic centimeters of blood. The icteric index was 40 units. The urine became sugar-free in two days and remained so with a diet of 160 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat with 45 units of insulin daily.

On March 6 a cholecystectomy was performed, and the common duct was drained through the stump of the cystic duct. A number of small faceted stones were removed. Subsequent analysis showed these to be composed of cholesterol and calcium bilirubinate. For one week postoperatively the patient had a low grade fever owing to infection of the wound caused by Bacillus pyocyaneus. Because of nausea he was unable to tolerate even a soft diet.

On March 8 the patient was given a regimen of alternate two hour feedings of 8 ounces (236 cc.) of milk and 8 ounces of orange juice with respective doses of insulin of 5 and 10 units. On March 10, because the urine contained from 2.5 to 4 per cent sugar, the doses of insulin were increased to 10 and 15 units, respectively, with the feedings kept as already mentioned. In the course of the next twenty-four hours the patient was given 40 ounces (1,180 cc.) of orange juice and 32 ounces (944 cc.) of milk, with 100 units of insulin, and at the end of this time the urine was free from sugar. On March 11 the dosage of insulin was sharply reduced. At 10 a. m. 10 units of insulin was given with 8 ounces of orange juice, at 2 p. m., 5 units of insulin with 8 ounces of milk, and at 6 p. m., 5 units of insulin with 8 ounces of milk. At 6:30 the patient suddenly became stuporous and could not be aroused. His eyes were set and glassy, the pupils did not react, and the pulse was weak and irregular. There were urinary and fecal incontinence and generalized twitchings, during which time the blood pressure rose to 210 systolic and 120 diastolic. Because of the difficulty encountered in trying to inject dextrose intravenously this episode lasted three fourths of an hour. There was prompt recovery after the intravenous injection of 15 cc. of 50 per cent dextrose. The patient was then able to swallow 8 ounces of orange juice. On the following day he was given a diet of 150 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat with 30 units of insulin. After twenty-four hours the urine was sugar-free. On March 20 the urine was sugar-free with the same diet but with no insulin. On March 29 the urine was sugar-free with 200 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat with no insulin. At this time the blood sugar after fasting was 120 mg., and the icteric index, 10. On April 4 readings for dextrose tolerance were:

Time	Blood Sugar, Mg. per 100 Cc.
9:05 (after fasting) (100 Gm. dextrose at 9:15)	65
9:45	96
10:15	141
11:15	118
12:15	92

Case 2.—A man aged 60 was admitted to the hospital on Feb. 22, 1934. There had been a sudden onset four weeks before his admission to the hospital with nausea and vomiting. Increasing jaundice developed, associated with moderate pruritus, acholic stools and very dark urine. The jaundice became progressively more intense. There was a loss of 14 pounds (6.4 Kg.) in four weeks. During this period there developed increasing thirst and polyuria. Urinalysis one week before admission to the hospital revealed the presence of sugar. On admission there was intense icterus and the edge of the liver was palpable 3 cm. below the costal margin. There was an enlarged, firm spleen. A provisional diagnosis was

made of biliary obstruction due to carcinoma of the head of the pancreas. The stool was acholic, and the urine contained 4.4 per cent of sugar. The total blood cholesterol was 1,165 mg. per hundred cubic centimeters, 750 mg. of this amount being in the form of esters. The icteric index was 105; the blood urea was 16 mg., and the blood sugar, 115 mg., per hundred cubic centimeters. The patient was given a diet of 200 Gm. of carbohydrate, 60 Gm. of protein and 40 Gm. of fat. At first it was impossible to control the glycosuria, even with 90 units of insulin daily. The concentration of sugar in the blood was 170 mg. The icteric index was 120. The value for amylase in the blood was 10.5 units. On March 2 the patient was given preoperative preparation with a continuous intravenous drip of a 5 per cent solution of dextrose, with 12 units of insulin for each 250 cc. of solution. He was operated on by Dr. Edwin Beer. A distended gallbladder and a hard nodule about half the size of a walnut in the head of the pancreas were found. There were no stones palpable in the common bile duct. A cholecystogastrostomy was performed. For the next three days a continuous intravenous drip of a 5 per cent solution of dextrose was administered. Eight units of insulin was administered for every 500 cc. of solution. During this period of continuous intravenous injection there were several attacks of disorientation accompanied by loud denunciation of those about him. On one occasion the temperature dropped to 97.4 F. On another occasion the sugar content was 25 mg. per hundred cubic centimeters of blood taken from one arm during continuous intravenous administration of dextrose. These symptoms disappeared on acceleration of the intravenous administration of dextrose. The administration of insulin was discontinued. During the next two days the urine contained 1.5 per cent sugar. The patient was then given a diet of 140 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat, with 45 units of insulin. On this regimen the urine was free from sugar. On March 7 the icteric index was 104; the total cholesterol content was 535 mg., and cholesterol esters, 310 mg., per hundred cubic centimeters of blood. By March 10 the icteric index had dropped to 68, the concentration of total cholesterol to 440 mg. and the esters to 235 mg. On March 17 the patient's urine was sugar-free, when the diet contained 140 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat with 10 units of insulin daily. The stool was well formed and soft; it contained urobilin. The icteric index was 45, the total cholesterol content, 440 mg. and esters, 290 mg. On March 21 the urine was sugar-free with a diet of 140 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat and no insulin. The concentration of blood sugar was 175 mg. per hundred cubic centimeters. The icteric index was 30, the total blood cholesterol, 470 mg., and esters, 340 mg. The amount of amylase in the blood, however, had risen to 31 units. On March 30 the urine was free from sugar with a diet of 200 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat and no insulin. The icteric index was 22, and the blood sugar content, 145 mg. The stools were dark and well formed. The patient's general condition was comparatively good. On April 2 he was given 1.5 Gm. of dextrose per kilogram of body weight with the following results:

Time	Blood Sugar, Mg. per 100 Cc.
After fasting	78
½ hour after dextrose	93
1 hour after dextrose	112
2 hours after dextrose	109
3 hours after dextrose	93

CASE 3.—A man aged 58 with no previous history of diabetes was admitted to the hospital for the first time on Jan. 14, 1934. For the past six weeks there

had been recurrent attacks of colicky pain in the right upper quadrant of the abdomen. Recently jaundice had appeared. There was an acute attack of pain, nausea and vomiting seven hours before admission to the hospital. On examination icterus was marked. The edge of the liver was palpable 2 inches (5 cm.) below the costal margin. Definite tenderness was elicited in the right upper quadrant. The urine contained 2.5 per cent sugar but no acetone. The blood pressure was 150 systolic and 70 diastolic, and there was evidence of cardiovascular disease. The stools were clay-colored. The content of blood sugar was 130 mg. and the total concentration of cholesterol, 275 mg., with cholesterol esters, 145 mg. per hundred cubic centimeters. The icteric index was 55, and the amylase in the blood, 12.5 units. The patient was given a diet of 250 Gm. of carbohydrate, 60 Gm. of protein and 40 Gm. of fat with 35 units of insulin. Control of the glycosuria was extremely difficult. There continued to be a 3 per cent excretion of sugar even when the dosage of insulin was raised to 90 units daily. As the clinical condition improved and the jaundice progressively diminished the sugar tolerance improved. The dosage of insulin was steadily reduced and then omitted. When the patient was discharged the icteric index was 12, and the urine was free from sugar with a diet of 300 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat and no insulin. The blood sugar after fasting was 120 mg.

The patient was seen three months later in the outpatient department. Two days before, he had been taken ill suddenly with acute abdominal pain in the right side radiating to the back and spreading diffusely over the abdomen. For two days the stools had been clay-colored and the patient had vomited once. There was slight icterus, and tenderness and rigidity were noted in the right upper quadrant. Tests of the urine gave positive results for bile and bilirubin. The urine contained 1 per cent sugar. A sugar tolerance curve was obtained the following day.

Time	Blood Sugar, Mg. per 100 Cc.
After fasting	95
½ hour after 100 Gm. of dextrose	190
1½ hours after 100 Gm. of dextrose	290
2½ hours after 100 Gm. of dextrose	230

The patient was admitted to the hospital the next day, May 5. The concentration of blood sugar was 130 mg. per hundred cubic centimeters. The total concentration of cholesterol was 250 mg. and the cholesterol esters, 50 mg. per hundred cubic centimeters of blood. The icteric index was 35. A direct van den Bergh test gave positive results, and an indirect van den Bergh test, 1 : 40,000. The stools were medium brown. The urine contained urobilin. The patient was under observation for two weeks. The glycosuria was controlled with a diet of 160 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat with 30 units of insulin daily. A laparotomy was performed on May 19. A large, abnormally brown, mottled liver was found. The gallbladder was distended and on aspiration foul, infected bile was obtained. No stones were palpable in the gallbladder or in the common bile duct. A cholecystostomy was performed. Postoperative biliary drainage was profuse, and the jaundice gradually disappeared, as did the urobilinuria. On May 24 the total cholesterol content was 250 mg. with traces of cholesterol ester. The icteric index was 27. By June 2 the icteric index had dropped to 18. On June 7 the total content of blood cholesterol was 235 mg. with an ester partition of 100 mg. The icteric index had dropped to 15, and the result of the indirect van den Bergh test to 1 : 300,000. During this time the tolerance for dextrose steadily improved. There was no postoperative glycosuria, and the

dosage of insulin was gradually reduced and finally omitted on June 1. On discharge the urine was sugar-free with a diet of 250 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat with no insulin. The blood sugar was 100 mg. per hundred cubic centimeters. On the twenty-first day postoperatively the cholecystostomy tube was removed and about a dozen faceted stones were extruded through the sinus. The tube was reinserted, and the wound was irrigated daily. Five days later the tube was removed permanently. The drainage diminished appreciably and the patient was discharged forty-two days after the operation in excellent general condition. The test for sugar tolerance on June 21 with 1.75 Gm. of dextrose per kilogram of body weight (93 Gm.) gave the following results:

Time	Blood Sugar, Mg. per 100 Cc.
After fasting	100
50 minutes after dextrose	165
2 hours after dextrose	160
3 hours after dextrose	100

COMMENT

Examination of the foregoing protocols reveals certain interesting features. In all three cases there was no clinical manifestation of diabetes mellitus before the onset of disturbance in the biliary tract. The patient in case 1 had been under observation in the hospital eight months previously. There had been no evidence of diabetes. In case 2 the onset of the diabetic symptoms coincided with the appearance of jaundice. It is, of course, less significant that there was no previous history of diabetes in case 3. In each of the 3 instances the development of symptoms of disturbance in the biliary tract with associated impairment of function of the liver, as measured by the icteric index and the elevated blood cholesterol, had been accompanied by hyperglycemia and glycosuria. Adequate biliary drainage, regardless of the nature of the lesion, resulted in the return of the icteric index and cholesterol in the blood to relatively normal values. With the restoration of function of the liver tolerance for dextrose steadily improved. The dose of insulin could be progressively reduced and the administration of the drug then omitted. Subsequent tests for sugar tolerance following the ingestion of dextrose then revealed nondiabetic values. This striking correlation between the function of the liver and dextrose tolerance was particularly noteworthy in case 3; the patient was observed during two episodes. In case 2 the biliary obstruction was due to carcinoma of the head of the pancreas. The improvement in the diabetic status closely followed the fall in the icteric index and the blood cholesterol after cholecystogastrostomy. This improvement in tolerance for sugar occurred at the same time that the amount of amylase in the blood rose from 10.5 to 31 units. The rise in value for amylase is said to indicate progressive pancreatic damage. However, at the time of this maximum concentration of amylase in the blood the urine was sugar-free when the

patient was given a liberal diet with no insulin and the dextrose tolerance curve was normal. If the glycosuria in biliary disease is to be explained on the basis of pancreatic damage no such inverse relationship would be anticipated.

Another interesting feature was the comparative resistance to insulin in cases 2 and 3 during the periods of marked impairment of the liver. The development of hypoglycemia postoperatively in cases 1 and 2 with relatively small doses of insulin seems paradoxical at first. These two findings can be reconciled most satisfactorily by a consideration of the blood sugar-regulating mechanism of the liver.

The level of sugar in the blood is maintained by a balanced equilibrium between the dextrose entering and the dextrose leaving the blood stream. The chief stores of the dextrose entering the blood stream are, first, the alimentary canal through the portal venous system and, second, the glycogen stores in the body, chief of which is the liver. Dextrose leaving the blood stream may go to the liver as the glycogen reserve; it may be burned directly in the resting metabolism of the tissues; it may go to the muscle and enter into reactions there or it may be converted to fat and stored as such. It is significant to observe that of the four chief processes into which dextrose enters after leaving the blood stream, only the first is reversible, the liver glycogen thereby being made available for the maintenance of the level of blood sugar.

When this equilibrium is disturbed at any one of its various points the end-result is either hyperglycemia or hypoglycemia, depending on the direction of the disturbance of the equilibrium. The liver is the chief organ concerned directly with the removal of dextrose from the blood stream as well as with its return to the blood stream when necessary. This regulation is under the control of antagonistic hormones, of which insulin and epinephrine are the most important, but in spite of the normal presence of hormones the liver itself must be functioning adequately to respond to the stimuli of these hormones. It will be noted that in case 1 insulin shock was accompanied by a sharp rise in blood pressure. This was probably due to the compensatory discharge of epinephrine in an effort to restore the normal level of blood sugar. The amount of epinephrine necessary to elevate the systolic blood pressure 90 mm. must have been enormous, but it apparently had no effect in overcoming the hypoglycemia. Loeb, Reeve and Glasier[15] pointed out that the rise in the content of blood sugar following the injection of epinephrine is less marked in persons with disease of the liver and diabetes than in normal persons, a finding, which is again

15. Loeb, R. F.; Reeve, E. B., and Glasier, H. P.: J. Clin. Investigation **10**:19, 1931.

consistent with the knowledge of the liver as a blood sugar-regulating mechanism. In totally hepatectomized animals epinephrine is not effective in overcoming the hypoglycemia.

The laparotomy in case 3 revealed a marked degree of hepatitis, which was consistent with the low values for cholesterol esters in the blood.[16] Similar observations in the case of Himsworth and in that of Baker and Rynearson have been cited. It is a common observation of pathologists that prolonged disease of the biliary tract results in extensive hepatitis, but it is, of course, equally true that biliary stasis may also be associated with pancreatitis.

In each of these cases when the patient was first seen the hyperglycemia and glycosuria necessitated a tentative diagnosis of diabetes. In case 2 this was confirmed by a test for dextrose tolerance. Following drainage of the biliary tract and the restoration of function of the liver, glycosuria and hyperglycemia disappeared in spite of a liberal diet, and the values for dextrose tolerance became normal. The normal reaction to the dextrose tolerance test is particularly significant in the interpretation of the disturbance of carbohydrate metabolism. Joslin has recognized its value in the differentiation of true diabetes but has warned of the danger of basing any clinical diagnosis on a single laboratory procedure. Peters and Van Slyke[17] stated that a normal response to the test may be accepted as fairly conclusive evidence against any degree of diabetes. Powelson and Wilder[18] found the simple test for dextrose tolerance to be a reliable means of differentiating benign glycosuria from true diabetes. Of 82 cases in which the diagnosis of normoglycemic glycosuria was made on the basis of this test, diabetes did not develop in any in the intervals of from one to twelve years that elapsed after the tests were made.

Although the normal reaction to the test for dextrose tolerance may be accepted as fair evidence for the exclusion of true diabetes, it does not rule out the possibility of other preceding transitory disturbances which might affect carbohydrate metabolism. However, neither temporary derangement of islet function nor infection can explain the favorable influence of biliary drainage in case 2. The carcinoma of the head of the pancreas remained intact, and the values for amylase in the blood indicated progressive pancreatic damage, although there was a complete restoration of dextrose tolerance. The striking direct correlation between sugar tolerance and liver function in each of the 3

16. Epstein, E. Z.: Cholesterol of the Blood Plasma in Hepatic and Biliary Disease, Arch. Int. Med. **50**:203 (Aug.) 1932.

17. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

18. Powelson, H. C., and Wilder, R. M.: Innocent Glycosuria, J. A. M. A. **96**:1562 (May 9) 1931.

cases reported here suggests the possibility that the glycosuria and hyperglycemia may not necessarily be manifestations of hypo-insulinism.

That the clinical picture of diabetes can exist with normal production of insulin and its attendant ability to oxidize dextrose is not a novel conception. Du Bois [19] and Sanger and Hun [20] have noted hyperglycemia and glycosuria in patients with hyperthyroidism who presented the clinical features of diabetes. Studies of the respiratory quotient, however, indicated that there was no impairment of the ability to oxidize carbohydrates. In an analogous manner it might be said that the clinical manifestations of diabetes encountered in these 3 cases of disease of the biliary tract may be interpreted on the basis of the associated disturbances of the function of the liver and that it may not be necessary to postulate the existence of hypo-insulinism. The recent development of the laboratory evidence of the function of the liver in the maintenance of the level of blood sugar offers a logical explanation of our observations.

The classic work of Mann, Magath and their associates [21] has demonstrated that the maintenance of the blood sugar is dependent on the presence of an adequately functioning liver. When the liver is removed from an animal there is a progressive decrease in the concentration of sugar in the blood to the point of hypoglycemia and death. This fact holds true in animals with an intact pancreas as well as in those which have been rendered diabetic by the previous removal of the pancreas. These experiments illustrate one phase of the function of the liver in the maintenance of the level of blood sugar, i. e., as the source which slowly but constantly releases the dextrose to maintain the normal concentration.

Pollack, Millet, Bollman and Wilder [22] demonstrated another function of the liver which has been confirmed by Soskin and his co-workers.[23] They subjected totally hepatectomized animals to the constant intravenous injection of dextrose. When the dextrose was injected at the rate of from 0.1 to 0.25 Gm. for each kilogram of body weight during each hour, a rate at which the animal can consume immediately practically all the dextrose so given, the values for blood sugar remained in the normal range. When, however, the rate of injection was such

19. Du Bois, E.: Clinical Calorimetry, Arch. Int. Med. **17**:915 (June) 1916.

20. Sanger, B. J., and Hun, E.: Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Oct.) 1922.

21. Mann, F. C., and Magath, T. B.: Effect of Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73 (July) 1922; ibid. **31**:797 (June) 1923. Mann, F. C.: Effect of Total Removal of the Liver After Pancreatectomy on the Blood Sugar Level, Medicine **6**:419, 1927.

22. Pollack, H.; Millet, R.; Bollman, J. L., and Wilder, R. M., Jr.: Proc. Staff Meet., Mayo Clin. **8**:557, 1933.

23. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: Am. J. Physiol. **109**:55, 1934. Soskin, S., and Allweiss, M. D.: ibid. **110**:4, 1934.

as to introduce 2 Gm. of dextrose for each kilogram of body weight during each hour, a rate which far exceeds the maximum rate of immediate utilization, then the values for blood sugar were in the range of those found in diabetic animals. Thus, the picture of diabetes, as far as the concentration of sugar in the blood and urine is a criterion, was reproduced by removal of the liver and giving dextrose at a rate beyond the maximum rates of immediate utilization. From previous studies on the respiratory quotient by Mann and Boothby [24] it was evident that there was no interference with the ability of these animals to oxidize dextrose. Hence, it can be said that these hepatectomized animals were not truly diabetic, even though their tolerance for dextrose indicated that this might be the case.

These remarks are in no way intended to depreciate the value of insulin in the maintenance of the normal carbohydrate cycle. The aforementioned experiments are based on the required presence of insulin. They do emphasize, however, that in spite of adequate amounts of insulin, unless the liver is capable of removing the dextrose from the blood stream the values for blood sugar will mount and hyperglycemia comparable to that found in cases of diabetes will occur.

The clinical significance of the liver in cases of disturbance of carbohydrate metabolism has long been recognized. In Claude Bernard's classic monograph "Leçons sur le diabètique" [25] he noted a most interesting case. His patient had had well developed diabetes mellitus for years. With the gradual onset of cirrhosis of the liver the clinical picture of diabetes disappeared. Bordley [26] at the Johns Hopkins Hospital recently noted a case of a similar condition. Extensive destruction of the liver by carcinoma, both primary and metastatic, has been reported from three different groups as being associated with marked hypoglycemia. Clinically these cases resembled those of hyperinsulinism, and yet on postmortem examination pancreatic disease was not found but there was destruction of the major part of the liver. Judd, Kepler and Rynearson [27] have reported 2 cases of spontaneous hypoglycemia. Biopsy on material from the liver in these 2 cases revealed obvious gross and microscopic damage. Hypoglycemia has been observed in patients with acute hepatitis caused by arsphenamine, acute yellow atrophy of the liver and thrombosis of the hepatic artery.

Disease of the liver not only may produce hypoglycemia but may cause resistance to insulin in persons known to have diabetes. This was

24. Mann, F. C., and Boothby, W. M.: Am. J. Physiol. **87**:486 (Dec.) 1928.

25. Bernard, C.: Leçons sur le diabète et la glycogenèse animale, Paris, J. B. Baillière et fils, 1877, p. 355.

26. Bordley, J. H.: Bull. Johns Hopkins Hosp. **47**:113 (Aug.) 1930.

27. Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: Am. J. Surg. **24**:345, 1934.

true in the cases reported by Pollack and Long [28] as well as in the one reported by Judd, Kepler and Rynearson. Resistance to insulin in cases of hemochromatosis after the development of cirrhosis of the liver is well known. Root,[29] Pollack [30] and MacBryde [31] have called attention to the rôle of the liver in the development of resistance to insulin. In Himsworth's case [12] of severe refractory diabetes autopsy revealed a grossly damaged liver and a normal pancreas.

SUMMARY

The experimental studies on the liver as a blood sugar-regulating mechanism are of significance in the interpretation of the hyperglycemia and glycosuria of disease of the biliary tract. In each of our 3 cases there was a direct correlation between the disturbance of carbohydrate metabolism and the degree of impairment of hepatic function. The restoration of normal function of the liver by adequate biliary drainage not only resulted in the disappearance of the diabetic manifestations, but the ingestion of dextrose was followed by normal values for sugar tolerance. The normal response to a test for sugar tolerance may be accepted as excluding true diabetes mellitus. The possibility of transient impairment of tissue of the pancreatic island will not explain the restoration of normal tolerance for sugar following biliary drainage in the case of carcinoma of the head of the pancreas. It is, therefore, suggested that the disturbance of carbohydrate metabolism in these 3 cases may be explained on the basis of a disturbance of the function of the liver as a blood sugar-regulating mechanism. Studies on the respiratory quotient should be carried out to determine whether there is actual impairment of the ability of these patients to oxidize dextrose.

One cannot deny the coexistence of disease of the gallbladder and true diabetes mellitus. The restoration of the normal value for dextrose tolerance is a criterion for differential diagnosis. It is, perhaps, significant that each of our patients was seen during his first attack of disease of the biliary tract. It is possible that repeated or prolonged attacks of disease of the biliary tract might produce permanent damage to the mechanisms regulating the blood sugar. It seems reasonable, especially in the light of recent experimental evidence, to assume that a disturbance of carbohydrate metabolism with complete restoration following biliary drainage as in these 3 cases may be interpreted on the basis of hepatic dysfunction.

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28. Pollack, H., and Long, E. P.: Thrombosis of the Hepatic Artery with Sudden Resistance to Insulin in a Diabetic Patient, Arch. Path. **13**:530 (March) 1932.

29. Root, H.: New England J. Med. **201**:201, 1929.

30. Pollack, H.: Proc. Staff Meet., Mayo Clin. **8**:453, 1933.

31. MacBryde, C. M.: Insulin Resistance in Diabetes Mellitus, Arch. Int. Med. **52**:932 (Dec.) 1933.

IDIOPATHIC STEATORRHEA

METABOLIC STUDY OF A PATIENT, WITH REFERENCE TO THE UTILIZATION OF NITROGEN AND FAT

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Steatorrhea is a prominent feature of a number of relatively uncommon diseases, among which may be mentioned sprue (tropical and nontropical) and celiac disease (Gee and Herter). In his recent monograph on idiopathic steatorrhea, Thaysen [1] attempted to prove that tropical sprue, nontropical sprue and celiac disease are manifestations of the same pathologic process. Others also have challenged the idea that sprue is a purely tropical disease and of restricted distribution. That the nontropical form of the disease is being more frequently recognized and reported is indicated by the articles of Thaysen,[1] Bennett, Hunter and Vaughan [2] and Mackie.[3] The last-mentioned author was able to collect reports of seventy-one cases from the literature. Other cases are known, and the condition is probably more common than is generally believed.

This syndrome must be distinguished from other types of diarrhea, among which is the type that is the result of pancreatic deficiency (external secretion). In the latter condition azatorrhea is also present, there is a greater loss of fat in the stools than there is in the idiopathic form, and the percentage of fatty acids is higher. In idiopathic steatorrhea the widespread nature of the systemic involvement (gastro-intestinal, hematologic, neurologic and metabolic) produces a variety of symptoms that are difficult to explain from a pathogenic standpoint. Similarly, there has been confusion regarding therapeutic procedures, especially the innumerable types of diet and the effects of vitamins, calcium, liver, iron, arsenic and hydrochloric acid. The results have

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1. Thaysen, T. E. Hess: Non-Tropical Sprue: A Study in Idiopathic Steatorrhoea, New York, Oxford University Press, 1932.

2. Bennett, T. I.; Hunter, Donald, and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease): A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anaemia, Quart. J. Med. **1**:603 (Oct.) 1932.

3. Mackie, Thomas T.: Nontropical Sprue, M. Clin. North America **17**:165 (July) 1933.

been variable. This all suggests that the pathogenesis of the disease is very uncertain. There are many symptoms that suggest a relationship to pernicious anemia. The work which has been done on sprue by Castle and Rhoads [4] and their associates indicates that the disease involves a deficiency of an intrinsic gastric factor. This result would seem to aid in discovering the disease process and in working out a therapy. Rhoads and Miller [5] pointed out that clinical sprue may arise in three ways: (1) by dietary lack; (2) by lack of the gastric enzyme that is absent in pernicious anemia, or (3) by inability to absorb the product of the interaction of the dietary and gastric factors. They admitted the emphasis which has been placed on the hematologic side, but they pointed out the simultaneous improvement in the lingual and gastro-intestinal symptoms, which was similar to that which had been observed by Minot and Murphy in pernicious anemia. They expressed the opinion that any dietary regimen that offers improvement does so by supplying an increased amount of the water-soluble vitamin, but in a very uncertain manner. These workers and others have demonstrated that the typical response of the reticulocytes occurs in sprue, as well as in pernicious anemia, when adequate amounts of the intrinsic factor are supplied.

Whether or not these observations are accepted, the fact remains that in steatorrhea an excess of fat occurs in the stools. In the literature, there is a controversy as to whether this condition is attributable to defective absorption, in spite of efficient hydrolysis, or to massive reexcretion of fat into the colon after the absorption in the small intestine has been relatively normal. In patients who were observed personally by Thaysen,[1] the output of fat for twenty-four hours varied from 15.9 Gm. to 66.7 Gm. The average was 36.59 Gm., which was about triple the average daily output for normal persons. The average loss, furthermore, was about a third of the fat which was ingested. He discovered that in individual cases the output of fat increased with increased intake of fats. Fatty acids made up the largest component of the output of fat; neutral fat came next, and the soaps were the smallest component. This, however, varied greatly in different cases and at different times. In most cases the output of nitrogen in the feces, for twenty-four hours, was below 3 Gm. These figures are in agreement with the analyses that have been published by other workers.

When the patient whose case is described in this report presented himself, an excellent opportunity was offered for a detailed study of the metabolism of fat and nitrogen, because the condition was well developed

4. Castle, W. B., and Rhoads, C. P.: The Aetiology and Treatment of Sprue in Porto Rico, Lancet **1**:1198 (June 4) 1932.

5. Rhoads, C. P., and Miller, D. K.: Intensive Liver Extract Therapy of Sprue, J. A. M. A. **103**:387 (Aug. 11) 1934.

and there were marked hematologic and neurologic symptoms. The patient was intelligent and cooperative.

Because of the loss of weight, the edema and the diarrhea, we hoped to be able to determine the time that was required to restore nitrogen balance, the extent of absorption of nitrogen, the extent of positive balance attained on a diet rich in protein and the effect of the diet on the serum protein content, the edema and the weight. The condition suggested a study of the output of fat when the intake was known and of the effect which was produced on the output by increasing the intake of the amount of fat which was excreted when diarrhea was controlled clinically and, finally, of any demonstrable effect on the rate of absorption after administration of liver extract, which obviously was indicated by the degree and type of anemia and by the neurologic changes.

REPORT OF A CASE

History.—A white man, aged 26, was seen first in March 1934. He had developed normally until the age of 15; since then there had been little growth. For the past ten years he had suffered recurring attacks of anorexia, diarrhea, bloating, abdominal discomfort, fatigue, loss of weight and pallor. The first two or three stools in the morning were bulky and gray; subsequent stools were watery. During the attacks from four to five stools were passed daily, and this persisted for a month or more. Between attacks, constipation frequently was present. In spite of the attacks, he continued through high school and entered a university, but after the first year he was forced to leave for two years. At that time he had his tonsils and appendix removed (at the age of 18). After some improvement he returned to the university and graduated in 1932, at the head of his class. However, since then he had been worse and was unable to work. The attack which caused him to come to the clinic had begun five months previously and was associated with numbness and tingling in the hands and feet and clumsiness and incoordination of the fingers, which had persisted for two months.

Two years before this attack he had a sore tongue and mouth for one month. Anemia was present at various times. His weight varied; the most he had weighed was 115 pounds (52 Kg.), but the usual weight was 110 pounds (50 Kg.). Various therapeutic agents had been tried; these included nourishing diets, fruit juices, dairy products, vitamins, iron, liver and hydrochloric acid.

Physical Examination.—The patient was 5 feet and 3 inches (160.02 cm.) in height and weighed 90 pounds (40.8 Kg.). He was definitely dwarfed and undernourished. Weakness, moderate pallor, moderate edema, clubbed fingers and a doughy, distended abdomen were prominent features. The gums disclosed reddened areas and bled easily. The pupils were irregular and unequal and did not react to light. Neurologic examination gave evidence of subacute combined sclerosis, which was well defined. Proctoscopic examination revealed mild proctitis. Roentgenologic examination of the gastro-intestinal tract disclosed a normal stomach and duodenum, slight dilatation and hypomotility of the small intestine and a spastic and slightly dilated colon. In the colon the haustral churning was absent distal to the hepatic flexure.

The urine was normal. The concentration of hemoglobin was 10.3 Gm. per hundred cubic centimeters (62 per cent); the erythrocytes numbered 2,580,000, and the leukocytes, 2,700, per cubic millimeter of blood. The differential count

was as follows: lymphocytes, 30 per cent; mononuclears, 6.5 per cent, and polymorphonuclear neutrophils, 63.5 per cent. There were 4.4 per cent reticulocytes. Macrocytosis, very slight poikilocytosis, moderate anisocytosis, slight polychromatophilia, Howell-Jolly bodies and basophilic stippling were present. In general, the blood smear presented the picture of pernicious anemia, but it lacked evidence of any shift of the neutrophils to the right. The stools were bulky, gray and pasty in appearance, but examination of fresh specimens did not show parasites. Serologic examination did not reveal syphilis. Analysis of the gastric contents disclosed total acidity of 38 cc. and free hydrochloric acid of 22 cc. of tenth-normal solution of sodium hydroxide. Roentgenograms of the skull, forearms, wrists and pelvis demonstrated slight osteoporosis. The value for urea was 28 mg. and that for sugar was 70 mg. per hundred cubic centimeters of whole blood. Quantitative determinations with the blood serum gave the following values: for calcium, 7.8 mg. per hundred cubic centimeters; for phosphorus, 3.4 mg., and for protein, 4.9 Gm. The value for cholesterol was 93 mg. per hundred cubic centimeters of plasma; that for lipoids, 379.4 mg., and that for fatty acids, 286.4 mg. The albumin-globulin ratio was 1.2:1. The concentration of bilirubin was 1.3 mg. per hundred cubic centimeters of serum, as shown by the indirect van den Bergh test. The bromsulphalein test of liver function gave normal results. The basal metabolic rate was — 3.

Course.—As a result of treatment, which consisted of the administration of a diet low in fat and high in proteins, calcium, viosterol and liver extract and which was carried out during the investigative procedures, there took place diuresis, disappearance of edema, a temporary decrease in weight that was followed by an increase, gain in strength, marked improvement in the gastro-intestinal condition, disappearance of evidence of inflammatory changes in the oral and the intestinal mucous membranes, typical reticulocytosis, improvement of the anemia and marked improvement in the neurologic symptoms and signs.

When the man was seen three months later, his weight was 104 pounds (47.2 Kg.), and his color was good. His bowels had been moving twice daily, morning and evening, and the stools were normal in color and consistency and were not bulky. There had not been any recurrence of edema or sore tongue. Paresthesia had practically disappeared, but the patient still tired easily. The concentration of hemoglobin was 12.9 Gm. (77 per cent); the erythrocytes numbered 4,320,000, and the leukocytes, 5,100, per cubic millimeter of blood. The blood smears revealed hypochromic anemia but did not disclose the features of pernicious anemia, which previously were present. The sensory disturbances were much improved, but no definite improvement was noted in the reflexes on neurologic examination.

Results.—During the first three periods of four days the average daily intake of protein was 82 Gm. With this intake the patient maintained a positive nitrogen balance from the start. The amount of retained nitrogen was high and was fairly uniform. With the increase of the intake of protein to 101 Gm. in the fourth period, the nitrogen balance increased to +3.73 Gm. This was a slight increase over the average of the preceding twelve days (+3.27 Gm.), but it was not as high as that which was obtained in the second period (+3.92 Gm.). In the fifth period the fat was materially increased for one day; however, the patient was unable to eat this food, and it had to be varied from day to day. The intake for this period, therefore, is not as accurately known as that for the other periods. With the clinical upset, there was a definite decrease in retention of nitrogen, although the intake of nitrogen was no less than it was in the first period. In the sixth period, the general condition of the patient was much better; he ate all

of the food, including the increased amount of fat and protein, and he had a very definite retention of nitrogen, which averaged 4.64 Gm. daily. It is difficult to state whether this was the result of the increased intake of nitrogen or of the change in the clinical condition of the patient. The daily amount of nitrogen in the feces was considerably higher than that which has been observed frequently as normal on a diet of a similar protein content. In spite of this rather high content of nitrogen in the feces, the patient was able to utilize sufficient protein to store considerable amounts.

During this period of moderately high intake of protein there were mild diuresis, disappearance of edema and some loss of weight. On continuation of the treatment after completion of the experiment, the weight gradually increased. The serum protein increased from 4.9 Gm. at the beginning of the experiment to 5.4 Gm. at the completion.

From a metabolic as well as from a gastro-intestinal standpoint, it is evident that the patient satisfactorily tolerated the high intake of protein and that this, combined with the other procedures, produced beneficial results.

With the low intake of fat (44 Gm. daily), the number of daily stools was reduced from three to one after the first two periods. Throughout the six periods excessive amounts of fat were present in the feces. Fowweather,[6] as the result of an investigation of the normal fat content of the stools of eighty-four adults, suggested that any specimen in which the total fat exceeds 28 per cent of the total dry matter is probably abnormal. In our case the fecal fat content definitely exceeded this value in all six periods, and the minimal excretion of fat was 33 per cent. With each increase in the daily intake of fat there were a decrease in the utilization and an increase in the output of fat. The amount of fat that was utilized, which was calculated from the difference between the intake and the output, varied relatively little with the intake except during the fifth period. Coincident with the marked gastro-intestinal upset which occurred in this period, there was a marked decrease in the utilization of fat. The small variations which occurred in the other periods suggest that, under these conditions at least, about 25 Gm. of fat is the maximal amount which can be utilized. With the increase in the output of fat the stools tended to become more frequent and became looser and bulkier. It was discovered that the patient could not tolerate 70 Gm. of fat daily but that 50 Gm. caused no marked disturbance.

Administration of liver extract produced reticulocytosis. This began early in the second period of observation and terminated in the fifth period. Whether the liver extract or the low intake of fat played the greater part in reducing the frequency of the stools in the third and fourth periods may be open to question, but we believe that it was the latter factor, because an increase in the intake of fat produced an increase in both the number and the size of the stools in spite of the continued effects of liver extract and its continued administration. If the intake of fat had been increased gradually before administration of liver extract, it is possible though improbable that there may have been a greater loss of fat in the stools. Furthermore, the positive nitrogen balance disclosed no changes which were parallel to the reticulocytosis.

Summary of Chemical Investigation.—The patient was placed in the hospital. The urine and feces were accurately collected in four day

6. Fowweather, F. S.: The Determination of the Amount and the Composition of the Fat of Faeces: I. Investigation of a "Wet" Method and Comparison with the "Dry" Method, Brit. J. Exper. Path. **7**:15 (Feb.) 1926.

periods and analyzed, as is shown in tables 1 and 2, to determine the daily output of nitrogen and the total lipoids. Diets were accurately weighed, and the intake of protein, of fat and of calories was determined by analysis.

The amount of nitrogen in the food, in the fat and in the feces was determined by the Kjeldahl method. The total fat was determined by the method of Kumagawa and Suto.[7] This is based on a preliminary saponification and followed by acidification, extraction with ethyl ether and finally reextraction with petroleum ether. It therefore includes the

TABLE 1.—*Showing Number of Stools, Weight of Patient and Reticulocyte Count*

Period	Date	Stools	Weight of Patient (Lb.)	Weight of Patient (Kg.)	Reticulocytes (per Cent)
I	March 12	3	93.0	42.2	2.3
	March 13	3	92.0	41.7	1.4
	March 14	3	91.5	41.5	1.5
	March 15	3	91.0	41.3	2.8
II	March 16	3	91.5	41.5	8.4
	March 17	2	92.5	41.9	10.2
	March 18	2	92.5	41.9	11.8
	March 19	2	91.0	41.3	10.6
III	March 20	1	91.5	41.5	....
	March 21	1	90.0	40.8	11.5
	March 22	1	89.25	40.5	11.2
	March 23	1	89.0	40.4	12.5
IV	March 24	1	89.25	40.5	6.5
	March 25	1	89.5	40.6	4.2
	March 26	1	90.25	40.9	3.5
	March 27	1	90.5	40.9	3.0
V	March 28	1	91.0	41.9	2.7
	March 29	1	89.5	40.6	3.2
	March 30	2	91.0	41.3	1.8
	March 31	1	91.0	41.3	1.5
	April 1	2	90.75	41.1	....
VI	April 2	2	92.0	41.7	2.3
	April 3	1	93.0	42.2	1.9
	April 4	2	92.5	41.9	2.6
	April 5	1	93.0	42.2	2.7

nonsaponifiable portion as well as the neutral fat, the soap and the free fatty acids. Daily determinations of creatinine were made to insure complete collections of the twenty-four hour specimens of urine.

The time of observation was divided into six periods of four days each. The first two periods were controls; in these, the average daily intake was 80 Gm. of protein, 44 Gm. of fat and sufficient carbohydrate to give a total of approximately 1,800 calories. In the third period, viosterol, 15 drops three times a day, and calcium lactate, 1 drachm (4 Gm.) three times a day, were added. Administration of these

7. Kumagawa, Muneo, and Suto, Kenzo: Ein neues Verfahren zur quantitativen Bestimmung des Fettes und der unverseifbaren Substanzen in tierischen Material nebst der Kritik einiger gebräuchlichen Methoden, Biochem. Ztschr. **8**:212, 1908.

continued throughout the experiment. In the fourth period the diet was increased to 101 Gm. of protein, 50 Gm. of fat and sufficient carbohydrate to supply a total of 2,080 calories. In the fifth period the diet was again increased, but there was a gastro-intestinal upset which prevented the patient from taking all his food and required reduction in the amount consumed. However, he recovered quickly, and in the sixth period he readily tolerated a diet of 122 Gm. of protein, 70 Gm. of fat and sufficient carbohydrate to furnish 2,646 calories.

TABLE 2.—*Showing Results of Chemical Examination of Stools and Other Data*

	Period I, March 12 to 15	Period II, March 16 to 19	Period III, March 20 to 23	Period IV, March 24 to 27	Period V, March 28 to April 1	Period VI, April 2 to 5
Intake of nitrogen, Gm. daily	12.34	13.22	13.22	16.14	12.56	19.49
Nitrogen in urine, Gm. daily	6.95	6.41	8.02	9.31	8.94	11.59
Nitrogen in feces, Gm. daily	2.08	2.89	2.61	3.10	2.89	3.26
Output of nitrogen, Gm. daily	9.03	9.30	10.63	12.41	11.83	14.85
Nitrogen balance	+3.31	+3.92	+2.59	+3.73	+0.73	+4.64
Total intake of fat, Gm. daily	38.90	40.20	40.20	47.30	35.60	66.60
Total output of fat, Gm. daily	13.50	15.10	19.40	23.90	21.30	39.00
Fat in feces, per cent of dry weight	36.60	32.70	39.90	40.60	39.10	50.00
Total fat utilized, Gm. daily	25.40	25.10	20.80	23.40	14.30	27.60
Weight of patient (beginning of period) (Kg.	42.20	41.50	41.50	40.50	41.30	41.70
Weight of patient (beginning of period) (Lb.	93.00	91.50	91.50	89.25	91.00	92.00
Preformed creatinine in urine, Gm. daily	0.319	0.295	0.308	0.313	0.294	0.320
Total calories in daily intake of food	1,812	1,812	1,812	2,080	.....	2,646
Diet*	1	1	1	2	3	3
Liver extract, daily	2 to 3 cc.			3 cc.		
			15 minims viosterol and 2 drachms (8 cc.) calcium lactate daily	Same medication	Not all food eaten the first day; diet 1 given the second, third and fourth days; diet 2 given on the fifth day	

* Diet 1 contained: protein, 80 Gm.; fat, 44 Gm., and sufficient carbohydrate to furnish a total of approximately 1,800 calories. Diet 2 contained: protein, 101 Gm.; fat, 50 Gm., and sufficient carbohydrate to furnish approximately 2,080 calories. Diet 3 contained: protein, 122 Gm.; fat, 70 Gm., and sufficient carbohydrate to furnish approximately 2,646 calories.

During the first period the patient received daily intramuscular injections of liver extract, which amounted to 13.5 cc. Nine cubic centimeters, in divided doses, was given during the fourth period. Daily estimation of the reticulocytes and frequent blood counts were made. Daily records of the weight, the volume of urine and the number of stools also were made.

COMMENT

In our clinical experience with cases of this type it has been apparent that little can be accomplished unless control of the diarrhea can be attained. Diet is an important factor in this consideration. Thaysen [1] has said that there is hardly any form of diet, from the most liberal

to the most restricted, that has not been recommended. Although the diets differ greatly, all have given good results according to various investigators. It also must be remembered that patients with this condition have a tendency to recover spontaneously from the attacks. Therefore, it is possible that the importance of diet has been overestimated. However, our observations in this experiment tend to confirm the principle that any diet should contain at least a low amount of fat. An excess of fat tends to pass through the intestine and carries with it calcium, phosphorus, vitamins and possibly some products of digestion of protein, in addition to causing the patient subjective discomfort and annoyance. A high intake of protein seems advisable for the following reasons: 1. The level of serum proteins must be maintained to prevent or relieve any nutritional edema. 2. An excess of nitrogen must be supplied to the tissues to overcome their depleted condition; the high nitrogen balance in this case suggests that there had been a previous loss of tissue proteins. 3. If the work of Castle [4] and his associates is accepted, the element of dietary lack may be overcome by an excess of the extrinsic factor which is of protein origin, and a high intake of protein of itself may be sufficient to maintain normal hematopoiesis in the milder cases.

SUMMARY

Data on a metabolic study of a case of nontropical sprue, which was featured by steatorrhea, diarrhea and hematologic, neurologic and nutritional changes, are presented. The loss of fat in the stools corresponds to that which has been reported by other investigators. A low tolerance for fat was present. When the intake of fat was increased, the amount of fat in the feces was increased. A low intake of fat reduced the frequency of stools to normal and relieved many of the gastrointestinal symptoms. With a moderately high intake of protein, the patient was able to store nitrogen in spite of rather high loss of nitrogen in the feces. An increase of the serum protein occurred with resulting diuresis, loss of edema and temporary loss of weight. Positive evidence of change in the absorption of fat or of protein did not result from the administration of liver extract in this case. The patient made marked clinical improvement as a result of the therapy used.

TULAREMIA

REPORT OF THREE FATAL CASES WITH AUTOPSIES

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Within a period of two years, three fatal cases of tularemia have been observed at the Johns Hopkins Hospital. It is my purpose in this communication to report the clinical and pathologic data furnished by these three cases. The account graphically illustrates the evolution of the recognition of a disease the identity of which has only recently been established.

The first patient died without a definite clinical diagnosis. Miliary tuberculosis seemed the most likely of the many diseases suggested, among which tularemia was not included. The pathologic changes were at first not definitely identified. The second case, occurring a year later, was diagnosed clinically only shortly before death, when a hitherto neglected primary lesion attracted attention. A more careful inquiry then elicited the story that shortly before the onset of his illness the patient had injured his thumb while skinning a wild rabbit. So strikingly did the results of the autopsy resemble those in the previous case that the identity of the disease in both was now apparent. Finally, after an interval of another year, a third patient was admitted to the hospital with a clinical picture so similar to that presented by the other two that tularemia was immediately suspected; and the suspicion was soon verified.

Up to the present time, autopsies on eighteen patients who died of tularemia have been recorded. From these the following important data are summarized (table):

Verbrycke [1] reported the case of a woman whose illness began with jaundice and who was operated on for disease of the gallbladder before the true nature of her ailment was recognized. The second and third cases were reported by Francis and Callender.[2] In one case the disease had a chronic course, and death occurred almost five months after the onset of the illness. Bardon and Berdez [3] contributed the account of the

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From the Medical Clinic, Johns Hopkins University and Hospital.

1. Verbrycke, J. R.: Tularemia, with Report of a Fatal Case Simulating Cholangeitis, with Postmortem Report, J. A. M. A. **82**:1577 (May 17) 1924.

2. Francis, E., and Callender, G. R.: Tularemia; Microscopic Changes of the Lesions in Man, Arch. Path. **3**:577 (April) 1927.

3. Bardon, R., and Berdez, G.: Tularemia: Report of a Fatal Case with Postmortem Observations, J. A. M. A. **90**:1369 (April 28) 1928.

Summary of Reported Cases of Fatal Tularemia with Autopsies

Case	Authors	Sex	Color	Age	Contact	Duration of Illness, Days	Clinical Characteristics	Pathologic Changes	Comment
1	Verbrycke	F	W	67	Rabbit	18	Jaundice	Lungs, spleen and lymph glands studded with nodules	
2	Francis and Callender	F	N	35	Rabbit	5 mo.	Chronic course	Lesions in lungs, liver, spleen and lymph nodes, some of which contained giant cells	
3	Francis and Callender	M	W	52	Fly bite	26	Terminal pneumonia	Spleen filled with nodules; surface of liver normal	Incomplete autopsy; only gross examination of liver and spleen
4	Bardon and Berdez	M	W	53	Rabbit	16	Bronchopneumonia	Lesions in lungs, spleen and liver	
5	Goodpasture and House	M	W	29	Rabbit	15	Generalized infection	Lesions in liver, spleen and lymph nodes	
6	Palmer and Hansmann	F	W	?	Rabbit	9	Rapid course	Lesions in liver, spleen and lymph nodes; lungs congested, but no foci of necrosis	
7	Simpson	M	N	25	Rabbit	4	Fulminant course	Lesions in lymph glands, spleen, liver and lungs	
8	Bunker and Smith	M	W	65	Rabbit	14	Bronchopneumonia	Lesions in lymph nodes, lungs and spleen	
9	Massee	M	W	40	Rabbit	18	Bronchopneumonia	Lesions in liver and spleen; confluent bronchopneumonia	
10	Haizlip and O'Neil	M	W	45	Rabbit and squirrel	18	Meningitis	Necroses in spleen; infarcts in lungs	Only gross pathologic examination made
11	Bryant and Hirsch	M	W	48	Rabbit	16	Meningitis	Miliary lesions in liver, lungs, spleen, lymph nodes, leptomeninges, ependyma and choroid plexus	
12	Permar and Maclachlan	M	N	36	Rabbit	17	Terminal pneumonia	Lesions in liver, lungs and lymph nodes	
13	Hartman	M	W	?	Rabbit	37	Encephalitis	Lesions in liver, lungs, spleen, lymph nodes and brain; none in meninges	
14	Foulger, Glazer and Foshay	F	W	37	Rabbit	22	Bronchopneumonia	Lesions in liver, lungs, spleen, lymph nodes and serosa of gastro-intestinal tract	Treated with convalescent serum
15	Blackford	M	N	38	Opossum	37	Abscess of the lung	Lesions in lungs, lymph nodes and liver	
16	Hartman, Beaver and Green	M	W	62	Rabbit	18	Generalized infection	Lesions in lungs, liver, spleen and lymph nodes	Diagnosed ten years after death
17	Gudger	M	W	32	Rabbit	31	Bronchopneumonia	Lesions in lungs and lymph nodes	
18	Gundry and Warner	M	W	53	Rabbit	17	Pneumonia	Lesions in lungs, liver, spleen and lymph nodes	
19	Bernstein	F	W	53	?	24	Bronchopneumonia	Lesions in lungs, liver, spleen and lymph nodes	Not diagnosed clinically
20	Bernstein	M	N	55	Rabbit	20	Bronchopneumonia	Lesions in lungs, liver, spleen and lymph nodes	
21	Bernstein	M	W	52	Rabbit	19	Bronchopneumonia	Lesions in lungs, liver, spleen, lymph nodes and tonsils	

case of a man who died sixteen days after injuring a finger while skinning a wild rabbit. Recent authors emphasize the frequency of pulmonary complications in the fatal cases of tularemia. The patient observed by Goodpasture and House,[4] however, gave no clinical signs of disease of the lungs. Similarly, in the case recounted by Palmer and Hansmann [5] there was no evidence of pulmonary involvement. Simpson's [6] patient died in less than five days after the onset of the disease—the most fulminant course yet reported. A physician, the history of whose illness was recorded by Bunker and Smith,[7] had terminal bronchopneumonia and pulmonary edema. Pneumonia, likewise, was the final event in the instance of a worker in Georgian produce markets whose case was reported by Massee.[8] Meningeal symptoms were the outstanding phenomena in the case reported by Haizlip and O'Neil.[9] The cerebrospinal fluid contained 2,100 cells per cubic millimeter. Bryant and Hirsch's [10] patient also presented the clinical picture of meningitis. There were 400 cells per cubic millimeter in the spinal fluid. Permar and Maclachlan [11] stressed the grave prognosis of that form of tularemia which is associated with diffuse pulmonary involvement, illustrating the assertion by their case. A third example of involvement of the central nervous system was reported by Hartman.[12] There were numerous focal necroses in the brain as well as evidence of meningitis. Foulger, Glazer and Foshay [13] described tularemic lesions in which Bacillus tularensis was demonstrated in stained sections. Blackford [14] recorded a fatal case in which the source of contagion was an opossum. Hartman, Beaver and

4. Goodpasture, E. W., and House, S. J.: The Pathologic Anatomy of Tularemia in Man, Am. J. Path. **4**:213, 1928.

5. Palmer, H. D., and Hansmann, G. H.: Tularemia: Report of a Fulminating Case with Necropsy, J. A. M. A. **91**:236 (July 28) 1928.

6. Simpson, W. M.: Tularemia; Study of Rapidly Fatal Case (Four Days, Seven Hours), Arch. Path. **6**:553 (Oct.) 1928.

7. Bunker, C. W. O., and Smith, E. E.: Tularemia; Report of Four cases, One Fatal, with Autopsy Report, U. S. Nav. M. Bull. **26**:901, 1928.

8. Massee, J. C.: Tularemia in Georgia; Report of a Fatal Case, J. M. A. Georgia **20**:66, 1931.

9. Haizlip, J. O., and O'Neil, A. E.: A Case of Meningitis Due to Bacterium Tularense, J. A. M. A. **97**:704 (Sept. 5) 1931.

10. Bryant, A. R., and Hirsch, E. F.: Tularemic Leptomeningitis; Report of a Case, Arch. Path. **12**:917 (Dec.) 1931.

11. Permar, H. H., and Maclachlan, W. W. G.: Tularemic Pneumonia, Ann. Int. Med. **5**:687, 1931.

12. Hartman, F. W.: Tularemic Encephalitis, Am. J. Path. **8**:57, 1932.

13. Foulger, M.; Glazer, A. M., and Foshay, L.: Tularemia; Report of a Case with Postmortem Observations and a Note on the Staining of Bacterium Tularense in Tissue Section, J. A. M. A. **98**:951 (March 19) 1932.

14. Blackford, S. D.: Pulmonary Lesions in Human Tularemia; Pathologic Review and Report of a Fatal Case, Ann. Int. Med. **5**:1421, 1932.

Green [15] reported a case of tularemia which occurred in Minnesota in 1921 but which was diagnosed only in retrospect after an interval of ten years. This probably is the earliest fatal case concerning which pathologic information is recorded in the American literature. Gudger [16] reported the case of a person with extensive areas of pulmonary consolidation in the absence of peripheral glandular enlargement. The most recent instance of fatal tularemia is that described by Gundry and Warner.[17]

REPORT OF CASES

CASE 1.[18]—M. E. G., a 53 year old white widow, was admitted to the Johns Hopkins Hospital on Dec. 8, 1930, complaining of vomiting and fever of twelve days' duration. There was a history of twelve operations: a hysterectomy and bilateral salpingo-oophorectomy, excision of a subsequent sinus tract, cholecystectomy and nine attempted repairs of a ventral hernia. The last operation had been performed in June 1930, at which time a general physical examination revealed nothing of note aside from the abdominal condition except moderate arteriosclerosis and a blood pressure of 200 systolic and 100 diastolic. The patient kept a boarding house in Baltimore and had not recently been out of the city.

Twelve days before admission, while cooking dinner, she suddenly fell to the floor, faint but not unconscious. A shaking chill lasting an hour followed, with continuous nausea and vomiting. Fever continued high for twelve days with constant vomiting so that she was unable to retain even water. Six days before entry her mouth and tongue became sore. Constipation was marked during the present illness.

On admission the temperature was 103.8 F., the pulse rate 94, the respiratory rate 18 and the blood pressure 148 systolic and 80 diastolic. She was moderately well nourished, acutely ill, and apathetic. The skin was dry. There was one questionable rose spot on the abdomen, and eczematous lesions were present over the buttocks. There was no pallor or cyanosis. There was no general glandular enlargement. The pupils reacted normally to light. The lips were dry. The tongue was heavily coated and the pharynx somewhat injected. The lungs were clear. The heart was not enlarged and was normal to auscultation. There was no abdominal distention. The liver and spleen were not palpable. Examination of the extremities and neurologic examination gave no remarkable results.

After admission the patient's progress was steadily downward. She continued to vomit, took fluids poorly and became progressively weaker. The temperature ranged from 102 to 105 F., with a terminal rise to 107.4 F. The striking developments were extreme cyanosis, which antedated and seemed much out of proportion

15. Hartman, H. R.; Beaver, D. C., and Green, R. G.: The Occurrence of Tularemia in Minnesota in 1921: Report of Two Cases—One Fatal with Necropsy Report, Minnesota Med. **16**:559, 1933.

16. Gudger, J. R.: Tularemic Pneumonia; Report of a Case, J. A. M. A. **101**: 1148 (Oct. 7) 1933.

17. Gundry, L. P., and Warner, C. G.: Fatal Tularemia: Review of Autopsied Cases with Report of a Fatal Case, Ann. Int. Med. **7**:837, 1934.

18. This case has been reported briefly by Hamman, L.: Clinical-Pathological Conference: A Case of Severe Anemia with Cardiac Manifestations; A Case of Obscure Infection, South. M. J. **26**:665, 1933.

to the signs of bilateral bronchopneumonia that appeared a week after entry, dyspnea without evidence of myocardial failure and an utter lack of localizing signs for what was clearly an overwhelming infection. On December 20, twenty-four days after the onset of the illness, the patient died of exhaustion.

Laboratory Data.—The results of blood counts were as follows:

	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Mononuclears, per Cent
12/ 8/30	90	5,740,000	9,720	72	18	10
12/ 9/30	..	.....	10,760	..	..	..
12/10/30	..	.....	12,120	..	..	..
12/11/30	86	4,280,000	18,000	79	19	2
12/14/30	75	3,910,000	12,050	87	8	5
12/18/30	66	3,820,000	14,200	88	7	5

The result of the Wassermann test on December 10 was negative; that of the flocculation test, doubtful. Chemical examination of the blood on December 20 showed: nonprotein nitrogen, 41 mg. per hundred cubic centimeters of blood; van den Bergh test, negative. Cultures of the blood on December 8, 9, 11, 12, 17 and 20 showed no growth. Cultures of the stools repeatedly gave negative results for the typhoid-dysentery group of bacilli but always showed occult blood. Examination of the urine revealed albumin (+), no sugar and occasional white blood cells. A culture was sterile. Agglutination tests gave the following results:

Agglutinations	Test	Results
Dec. 8, 1930	Widal	Negative
Dec. 10, 1930	Widal	Negative
Dec. 11, 1930	Widal	Negative
Dec. 12, 1930	Widal	Negative
Dec. 16, 1930	Widal	Negative
	For B. melitensis	Negative
Dec. 17, 1930	Weil-Felix	Negative

On June 18, 1930 (previous admission) the teleoroentgenographic measurements were median right 3.5, median left 9.6, and thoracic 26.1 cm. Roentgen examination of the chest showed the lungs clear and the heart and aorta within normal limits. On December 10 and 12 (present admission) the lungs were clear. On December 18 there was evidence of bronchopneumonia in the left lung.

The pulse rate varied from 90 to 130 and the respiratory rate from 24 to 50; the blood pressure, which was low on entry, rose to 218 systolic and 75 diastolic at the end.

The clinical diagnosis was miliary tuberculosis (?), typhoid (?) and bronchopneumonia.

Autopsy.—The autopsy was performed twenty-one hours after death by Dr. F. B. Kindell.

Macroscopic Examination: The body was that of a well nourished middle-aged white woman. There was rigor mortis of the extremities. The scleras were pale. There was slight edema of the ankles. A long scar was present in the midline of the abdomen. The rectus muscles were separated about 3 cm., but there was no hernial pouch.

There were adhesions about the gallbladder and between the intestine and the abdominal wall near the scar of the operative incision. There were dense adhesions about the site of the hysterectomy. There was no free fluid in the abdominal cavity.

The left pleural cavity contained 150 cc. of bloody fluid. The posterior and inferior pleural surfaces were covered by a fibrinopurulent exudate with numerous areas of hemorrhage. There were no old adhesions. There was no free fluid in the right pleural cavity. Over the lower lobe of the right lung there was a fibrinopurulent exudate like that on the left. The pericardial cavity was normal.

The heart weighed 320 Gm. The epicardium was smooth. The auricles contained no thrombi. All the valves were normal. The myocardium showed no gross scars. The coronary arteries were patent. They showed only slight arteriosclerosis.

The lungs were for the most part air-containing. The pleural surfaces of the upper lobes were smooth. There were no apical scars. The posterior and lateral

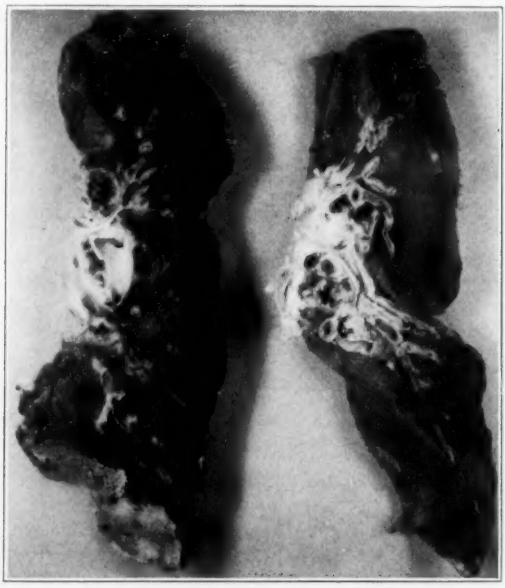

Fig. 1 (case 1).—Macroscopic view of the lungs, showing caseous glands at the hilus and fibrinous pleurisy. (The photographs shown in figures 1 to 6 were made by Mr. Milton Kougl.)

surfaces of both lower lobes were covered by a layer of edematous yellow fibrin, in places from 2 to 3 mm. in thickness. The pleural surfaces were dull and granular with numerous flecks of hemorrhage. Scattered gray nodules could be seen beneath the pleura. On scraping away the surface layer of fibrin, very tiny granules could be seen, suggesting tubercles.

On section the lower lobes of both lungs contained scattered tubercle-like nodules. Often these attained a size from 5 to 6 mm. and were made up of groups of confluent smaller nodules. There were a few larger patches of gray consolidation suggesting those seen in caseous pneumonia. One such firm area measured 3 cm. in width. It occupied the posterior upper part of the left lower

lobe and came to the pleural surface. The rest of the tissue of this lobe was red, soft and elastic. The upper lobes were more distended with air and gray-pink. Only an occasional tubercle-like nodule was seen on the cut surface.

The peribronchial nodes were enlarged. Two or three were caseous and softened. One at the hilus of the left lung was 2.5 cm. in diameter. It contained a central firm nodule from 5 to 6 mm. in diameter, which was hyaline and pigmented, suggesting an old scarred lesion. The peripheral portion of the node was white and caseous, and in part the material was soft and semifluid. Other nodes showed good-sized peripheral caseous masses.

The spleen weighed 320 Gm. It was enlarged and soft. The delicate capsule tore readily. The surface was dull and finely granular. On section the surface was studded with gray or yellowish nodules varying in size up to 4 and 5 mm.

The mucosa of the intestines showed no lesions. No ulcers or source of hemorrhage was found. The colon was the site of a number of small diverticula. The mesenteric nodes were not enlarged, and no caseous nodules were found.

There were scattered punctate hemorrhages in the gastric mucosa, but no gross ulcers. The mucosa of the duodenum was normal.

The pancreas was normal.

The liver weighed 1,600 Gm. The capsule was smooth. The liver was softer than usual. On section the lobulation was accentuated. The center of each lobule contained a yellow opaque fleck, or in other places a red spot, while the periphery was paler red-brown with a slight yellowish tinge. There were numerous scattered nodules, often 2 mm. in diameter.

The gallbladder contained eight stones, which were very much alike in size and shape, measuring 12 by 12 by 15 mm. as a rough average. They were pyramidal, with concave surfaces and smaller facets near the corners. The wall of the gallbladder was not thickened. No stones were found in the bile ducts, which were not distended.

The adrenal glands and kidneys were normal.

The bladder was tied down by adhesions and was normally adherent to the pelvis. Its wall was thin, and the mucosa showed no lesions. The cervix of the uterus was all that remained. There were no remarkable findings on section.

The pharynx and larynx were normal. The thyroid gland was not enlarged and was normal on section. Two caseous nodes were found near the bifurcation of the trachea.

The aorta showed considerable arteriosclerosis. There were elevated plaques about the intercostal arteries. The thoracic aorta showed much more longitudinal wrinkling of the intima than usual, which in one or two places became a radiate pucker suggesting aortitis, but there was no other evidence to support this.

The bone marrow of the femur contained rather large islands of red hyperplastic tissue.

One large caseous node at the hilus of the liver measured 3.5 by 2 cm. This one on section was completely caseous, and the contents were in part soft and viscous. A second smaller node, 1.5 cm. in diameter, which was also caseous and soft, was found near the pancreas. No other caseous abdominal lymph nodes were found. A small node, 1 cm. in diameter, was found near the aorta behind the pleura. No grouping of nodes about the thoracic duct was present to suggest a lesion there, and the duct itself was normal in appearance.

Microscopic Examination: Study of the heart showed that the muscle fibers were atrophic, many of the cells contained more pigment than usual, and there were more nuclei and cells in the interstitial tissue than usual.

Three sections of the lungs showed an organizing fibrinous or fibrinopurulent pleurisy. There was a rather fresh lesion which was quite like that seen in tuberculous lobular pneumonia, with fresh necrosis and caseation. Many of the areas were rather compact and hyaline. No tubercle bacilli were seen in stains of these sections. One of the sections showed the two older caseous nodules in the lower lobe of the left lung. In the center these were hyaline and pigmented but still not extremely old. There seemed to be a spread of these lesions with a fresher process in the periphery. No tubercle bacilli or other bacteria were found on careful search.

In the spleen there were a few caseous nodules with fragmented material in the center and narrow hyaline capsules. No tubercle bacilli or other bacteria were found in the lesions on most careful staining and search.

There was rather marked atrophy of the central liver cells, and an occasional necrotic cell was seen. There were a few caseous areas, which showed beginning encapsulation. No bacteria were revealed by any stain.

The tubular epithelium of the kidneys was ragged and granular.

In the aorta there was arteriosclerosis but nothing to suggest syphilis.

One section made of the lymph nodes was from a bronchial node. The other two showed the softened nodes at the hilus of the liver. The first contained an older, quite hyaline lesion. All showed fresh caseation, and one showed a caseous lesion extending into the surrounding fat. Smears from these nodes showed no tubercle bacilli, even after concentration with sodium hydroxide. No other bacteria were found.

The bone marrow of the femur showed considerable hyperplasia.

Further stains for bacteria, including stains for tubercle bacilli and Nicolle's tannic acid-methylene blue stain for glanders, failed to show any organisms.

A summary of Dr. MacCallum's notes is as follows: The lungs, liver, lymph nodes and spleen showed areas which at first sight looked like an acute tuberculous necrotizing process. No actual tubercles were seen, however, and no lesions which might be regarded as typically tuberculous. Above all, no tubercle bacilli were found after the most careful staining and search.

Bacteriologic Studies.—A smear of the heart blood showed no organisms. From a culture no organisms resembling B. tularensis were grown.

A guinea-pig inoculated in the groin with material from an abdominal lymph node did not die. However, the gland had been kept in the icebox for a period preceding the inoculation.

Anatomic Diagnosis.—The diagnosis was: tularemia; caseous lobular pneumonia; bilateral pleurisy (fibrinopurulent); caseous peribronchial and peritracheal lymph nodes; large caseous lymph nodes at the hilus of the liver and near the pancreas; caseous foci in the liver and spleen; cholelithiasis; peritoneal adhesions; evidence of a hysterectomy; diverticula of the colon; areas of encephalomalacia and calcified vessels in the globus pallidus.

CASE 2.[19]—F. P., a 55 year old Negro laborer, was admitted to the Johns Hopkins Hospital on Dec. 31, 1931, complaining of shortness of breath, chills and fever. The patient's condition was such that a satisfactory history was never obtained from him, but apparently his general health had been excellent in the past. He had suffered from occasional headaches and from nocturia (urinating two or three times a night) for several years. His recent work had been that of a day laborer on a farm.

19. The history is given here in the manner in which the details were divulged rather than in the true chronological order.

Two weeks before admission he contracted a cold and cough, which were severe enough to prevent him from working but did not cause him to go to bed. Four days later he had a chill. Breathing became difficult. Eight days before entry the urine became "black," and it remained so until the day before admission, when it became reddish. Three days before, the cough became productive of yellowish sputum. The patient now went to bed. On the following day he complained of dizziness and had bouts of delirium. During the two weeks before admission he vomited only once and probably had some fever, but no sweats.

On admission the temperature was 102.2 F., the pulse rate 124, the respiratory rate 44 and the blood pressure 130 systolic and 80 diastolic. He was acutely ill, delirious and disoriented. There was marked cyanosis, with rapid, shallow respirations. He had an occasional unproductive cough. There was questionable stiffness of the neck. The tongue was coated. The throat could not be examined. The epitrochlear glands were palpable, but the other peripheral lymph nodes were not enlarged. The lungs showed impairment of the percussion note below the angle of the scapula on the left, with suppression of breath sounds over the same area. In both axillae there were many fine moist râles. The heart did not seem enlarged. The sounds were somewhat obscured by pulmonary noises. There was a progression of arrhythmia, bigeminy, pulsus paradoxus and auricular fibrillation following closely on one another. The abdomen was moderately distended. The liver was enlarged 2 fingerbreadths to percussion, but the edge was not felt. The spleen was not felt. Neurologic examination gave no remarkable results aside from a possible Kernig sign.

On the day after admission the patient appeared somewhat improved. The symptoms were still predominantly pulmonary. The condition in the chest had changed little save that the breath sounds showed more prolongation of expiration over the lower lobe of the left lung. A lumbar puncture yielded normal spinal fluid. The fever ranged between 103 and 105 F. The situation was essentially the same on the following day. There were diffuse pulmonary signs without definite evidence of consolidation. Delirium continued. At this time it was discovered that the right epitrochlear gland had become enlarged to a diameter of 3 cm. Further investigation disclosed an apparently healed lesion on the ball of the right thumb, which, however, was tender to pressure. Further questioning of the patient's family yielded the information that one week before the onset of the present illness he had skinned and cleaned three or four rabbits, during which process he had pierced his right thumb with a bone. Subsequently the thumb had become sore, so that on two occasions during the first week of his illness it had been punctured with a needle by the patient's sister and pus had been obtained. With this new guide, further tests were carried out, and the patient's serum was found to agglutinate the tularemia antigen. From then on he became rapidly worse. He sank into coma and showed progressive signs of intoxication. Generalized râles developed in the lungs, and purulent conjunctivitis of the right eye appeared. Cyanosis was extreme, the cardiac arrhythmia continued, and he died on Jan. 5, 1932, the twentieth day after the onset of the acute illness.

Laboratory Data.—The results of blood counts were as follows:

	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Mononuclears, per Cent
12/31/31	88	4,230,000	6,880	27	61	12
1/ 1/32	..	.....	4,280	..	..	..
1/ 2/32	..	.....	4,920	..	..	..
1/ 3/32	..	.....	5,120	..	..	..
1/ 4/32	..	.....	5,920	76	22	2

The Wassermann reaction on January 1 was negative; the flocculation test gave negative results.

Examination of the cerebrospinal fluid showed 1 cell per cubic millimeter. The Pandy and Wassermann reactions were negative.

Chemical examination of the blood on January 2 showed nonprotein nitrogen, 50 mg. per hundred cubic centimeters, and carbon dioxide-combining power, 42.8 volumes per cent; on January 4, nonprotein nitrogen, 69 mg. per hundred cubic centimeters, and carbon dioxide-combining power, 43.8 volumes per cent.

Cultures of the blood on Dec. 31, 1931, and on Jan. 2, 1932, showed no growth.

A smear showed that the sputum did not contain tubercle bacilli. A culture revealed Staphylococcus aureus and beta hemolytic streptococci.

The urine was reddish and contained albumin (++), no sugar and occasional white blood cells. Spectroscopic examination showed hemoglobin to be present (the benzidine reaction was negative). The results of agglutination tests were as follows:

Agglutinations	Test	Results
Jan. 2, 1932	Widal	Negative
	For B. tularensis	Positive, 1:160 (dilution carried no higher)
Jan. 4, 1932	For B. melitensis	Negative

Material from lesions, glands and blood was examined. On January 3 a smear was made of pus from the right thumb, but the results were negative. Pus was taken from a gland in the right epitrochlear region for a smear, which showed suspicious gram-negative bacilli. A culture produced no growth. A guinea-pig given an injection of blood taken from the patient died in two days. Autopsy showed multiple necroses in the liver and spleen.

An electrocardiogram made on January 4 showed normal sinus rhythm, sinus tachycardia and an upright T wave in all leads.

On December 31 roentgenograms of the chest revealed diffuse infiltration of both lungs, possibly bronchopneumonia; on January 2 small areas of bronchopneumonia and the mediastinal shadow enlarged owing to dilatation of the aorta.

The pulse rate varied from 48 to 160; the respiratory rate, from 24 to 52, and the temperature, from 102.2 to 105.6 F.

The clinical diagnosis was tularemia, bronchopneumonia and arteriosclerosis.

Autopsy.—The autopsy was performed four hours after death by Dr. G. Fite.

Macroscopic Examination: The body was that of a well nourished Negro of middle age. There was moderate rigor mortis. The head, eyes and ears were normal. There was no edema. There were no cutaneous lesions except an incised wound on the ball of the right thumb, exuding a little necrotic material. A large lymph node lying just above the elbow had been punctured by a needle.

Both pleural cavities contained a little fibrinous exudate, most of which was plastered on the surfaces of the lungs. There was no fluid. There were numerous small hemorrhages.

The heart weighed 360 Gm. The right auricle seemed quite large. The right ventricle was not particularly hypertrophied, although it might be somewhat dilated. The pulmonary valve was normal, and so was the mitral valve. There were minute grayish opacities here and there in the musculature of the left ventricle, and the endocardium was thickened throughout. The aortic valve was normal.

The pleural surfaces of the lungs were flecked with fibrin. There were scattered areas, sometimes quite large, of lobular pneumonia. The bronchi were reddened and roughened. Some of the areas of lobular pneumonia were small and

sharply outlined and on the cut surface had a smooth, uniformly gray appearance. The lymph nodes at the hilus were not particularly enlarged. One of them showed old gray scars suggesting tuberculosis.

The liver was large, weighing 1,900 Gm. Scattered through it one could see a few sharply outlined gray or yellowish-gray nodules, 1 or 2 mm. in diameter. On careful inspection these seemed to be numerous. The centers of the lobules in many places appeared to contain more blood than was normal. The capsule of the liver was smooth.

The spleen was considerably enlarged, weighing 500 Gm. Its surface was studded with myriads of small caseous nodules similar to those in the liver. Beneath the capsule one could see many white and yellowish-gray areas varying in size from a pin point to 6 or 7 mm. in diameter, and on section these areas were plainly seen on the cut surface, studding the organ almost uniformly throughout.

The kidneys were normal in size. The capsule came away, leaving a perfectly smooth surface, and on section the architecture appeared normal.

The pancreas was normal. The lymph nodes about the pancreas were large and contained gray nodules.

The adrenal glands were large. They had a very darkly pigmented zone outside the medulla.

There was an ulceration in the esophagus just at the region of the bifurcation of the trachea. This was about 1 by 0.5 cm., was rather sharply outlined and had a greenish base. There were roughening and reddening of the trachea at the bifurcation, and a diphtheritic-like exudate covered the surface. It was not ulcerated, and the ulcer in the esophagus was not related to any lesion in the underlying trachea.

The aorta was somewhat sclerotic.

The large epitrochlear lymph node on the right side on section contained a large abscess, measuring about 1 cm. in diameter. There were in it also numerous small caseous nodules. The large lymph nodes in the axilla on the right side had much the same appearance. Several of them contained caseous areas. A few of them had the appearance of abscesses. The lymph nodes in the left axilla and in both groins were not altered, except for one scarred and pigmented node in the right inguinal region.

There were large lymph nodes about the bifurcation of the trachea. These were anthracotic and had gray flecks and streaks through them, suggesting an old tuberculous process. On the right side of the neck just below the thyroid gland there was a very large mass of anthracotic lymph nodes which were flecked throughout with gray. This mass measured about 7 cm. in length and lay just lateral to the trachea. The lymph nodes were all separate from each other, and higher up there were still others, enlarged, anthracotic and flecked with gray, which were rather firm. On the opposite side, there were some small lymph nodes which had the same general character. On one side there was a fairly large hilar lymph node of the same character.

The bone marrow of the femur was fatty. There were small yellow opacities in the bone marrow of the vertebrae. The meninges were rather cloudy over the surface of the brain and, indeed, over the temporal lobes as well. This did not appear to be a fresh exudate of any sort but rather resembled a thickening of the meninges themselves. There was perhaps slight atrophy of some of the convolutions. The brain was normal in several sections.

Microscopic Examination: The lesions characteristic of tularemia were seen abundantly in the lungs, liver and spleen and in lymph nodes from all regions of the body. They closely resembled very soft caseous tubercles, with necrotic

centers filled with débris and surrounded by margins of better preserved mononuclear cells. There were a good many polymorphonuclear leukocytes about some of the foci, especially in the spleen. These were exceedingly numerous in the spleen and were of quite irregular pattern and variable in size. Giant cells were rarely found. Only one was seen in the spleen. The distribution of the lesions apparently bore no relation to the anatomic structure in any organ. In the epitrochlear lymph nodes, the lesions had coalesced to form a fairly large abscess.

In the skin of the thumb, the same sort of lesion was seen, with many mononuclear cells.

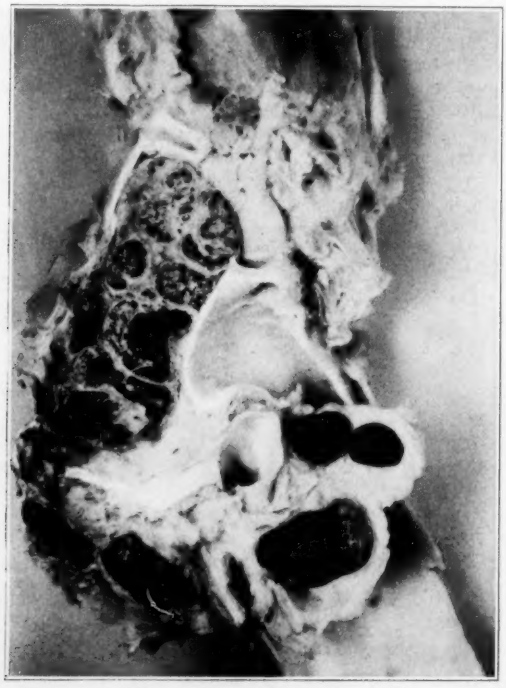

Fig. 2 (case 2).—Mass of caseous anthracotic lymph nodes about the aorta.

The lungs showed beautifully the lesions of tularemia, with areas of necrotic pneumonia, which resembled tuberculous caseous pneumonia very closely, except that they did not in any way suggest distribution by aspiration, and the lesion destroyed the lung tissue throughout its extent. Closely mingled with these lesions were areas of lobular pneumonia due to the pneumococcus (type II) which was seen in abundance in bacterial stains.

No Bacilli tularensis were stained in the section in spite of many diverse attempts both on tissue fixed in formaldehyde and Zenker's solution and on frozen sections.

Bacteriologic Studies.—A smear of the heart blood showed no organisms, and a culture was sterile. A smear of material from the spleen showed no organisms, and a culture was sterile. A culture of lung tissue showed pneumococcus (type II).

Anatomic Diagnosis.—The diagnosis was as follows: tularemia; a necrotic wound in the right thumb; caseous nodules and abscesses in the right epitrochlear and the axillary lymph nodes; caseous miliary nodules in the spleen and liver; extensive caseous lobular pneumonia; acute fibrinous pleurisy, and hemorrhages in the pleura.

CASE 3.—T. B. F., a 52 year old white man, a nail inspector, was admitted to the Johns Hopkins Hospital on Dec. 1, 1932, complaining of chills and fever. His past health had always been excellent. Two and a half weeks before, he shot and skinned a wild rabbit. At the time there was an unhealed cut from an accidental injury on his right thumb. Three days later he was seized with a chilly sensation, and anorexia developed. Nine days before admission he became weak and feverish. Four days later, he was compelled to go to bed, when drowsiness and apathy were striking. Three days before admission, frontal headache appeared along with a sore throat and increasing constipation. His temperature was found to be 103 F. From then on he became rapidly weaker and was almost constantly delirious.

On admission his temperature was 104 F., the pulse rate 130, the respiratory rate, 30, and blood pressure 120 systolic and 65 diastolic. He was a large man, acutely ill, delirious and uncooperative. There was extreme cyanosis of the mucous membranes, as well as great dyspnea and orthopnea. He was sweating profusely. The scar of a cut on the ball of the right thumb was incompletely healed. There were no palpable glands save in the left cervical chain. His tongue was very red and deeply fissured. There were patches of grayish exudate with a hemorrhagic base on the soft palate. Breathing was labored but regular. There was moderate emphysema. Both lungs were filled with moist râles without any definite evidence of consolidation. The pulse was rapid. The heart sounds were obscured. There was a loud apical systolic murmur. Marked abdominal distention was present. The liver and spleen were not palpable. There was slight edema of the ankles. The neurologic examination gave negative results.

The use of an oxygen tent gave some relief. However, all of the symptoms present on entry persisted, while the patient became rapidly more prostrated. Distention was combated with difficulty. He was unable to void. There was an occasional unproductive cough. Several days after admission a pustule developed at the center of the lesion on the thumb. At the same time an enlarged gland was felt in the right axilla. Subsequently this became larger and fluctuant. With increasing tachycardia, unabated dyspnea and cyanosis and continued sweats, the patient died on Dec. 5, 1932, nineteen days after the onset of his illness.

Laboratory Data.—The results of blood counts were as follows:

	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Mononuclears, per Cent
12/1/32	86	4,000,000	10,250	80	20	..
12/2/32	..	.....	9,600	..	..	..
12/3/32	..	.....	7,300	81	17	2
12/4/32	..	.....	3,550	75	21	4

The Wassermann reaction on December 1 was negative. The flocculation test gave negative results. Chemical examination of the blood on December 3 showed

36 mg. of nonprotein nitrogen per hundred cubic centimeters of blood. The van den Bergh indirect test showed a faint trace.

Cultures of the blood on December 1 and 3 showed no growth.

A culture of the stools gave negative results for the typhoid-dysentery group of bacilli. The guaiac test gave a positive reaction.

The urine contained: albumin ++, no sugar and occasional white blood cells and granular casts. A culture showed no growth. The results of agglutination tests were as follows:

Agglutinations	Test	Results
Dec. 1, 1932.....	Widal	Negative
	For B. tularensis	Positive, 1:80
Dec. 2, 1932.....	For B. melitensis	Negative
Dec. 3, 1932.....	For B. tularensis	Positive, 1:160
Dec. 4, 1932.....	For B. tularensis	Positive, 1:320

A guinea-pig given an injection of the patient's blood on December 2 died in two days. Autopsy showed multiple focal necrotic lesions in the spleen and liver.

On December 2, also, roentgenograms of the chest showed both lungs extensively solidified.

The pulse rate varied from 130 to 180; the respiratory rate, from 24 to 42, and the temperature, from 99 to 104.2 F.

The clinical diagnosis was tularemia and pneumonia.

Autopsy.—The autopsy was performed three hours after death by Dr. E. Henriksen.

Macroscopic Examination: The body was that of a well nourished, well developed white man. There was very slight rigor mortis. On the right thumb there was a well healed scar near the tip.

There was no free fluid in the abdominal cavity. The peritoneal surfaces were smooth.

There was no free fluid in either pleural cavity. The pleural surfaces were rough and covered with a fibrinopurulent exudate, more marked at the base of the right lung. There were fine adhesions over the entire lateral and posterior aspects of both lungs.

The heart weighed 425 Gm. The endocardium and myocardium appeared normal. The valves were all essentially normal, except for the aortic valve, in which there was slight thickening of the border of each cusp. There was a moderate degree of arteriosclerosis of the aorta and its branches.

The lungs were bulky. There was a whitish layer of fibrin on the posterior surface of the lower lobe of the right lung. The whole pleural surface was dull and granular, with good-sized patches in which hemorrhage had occurred. White areas shone through the pleura and stood out above the surface.

On section there were large white opaque areas of consolidation. These stood out on the cut surface and were very sharply outlined, with areas of hemorrhage about some of them. They were so opaque as to suggest caseous lesions. The swollen peribronchial lymph nodes contained white caseous areas. The bronchi were reddened and roughened. There were in addition to these lesions, edematous, reddish, softer pneumonic areas.

The spleen weighed 125 Gm. The capsule was wrinkled, and there were numerous small gray flecks sprinkled over the entire surface. On section the pulp was soft, dark and purplish red, with several small necrotic nodules scattered through it.

The intestines were normal.

The pancreas was normal.

The liver was somewhat enlarged, weighing 2,100 Gm. The lobulation was accentuated. On the cut surface, sharply outlined small opaque nodules could be seen. They resembled small tubercles, some of them being almost 1 mm. in diameter.

Together the adrenal glands weighed less than 5 Gm. On section the medulla was gelatinous. The cortex, however, was well outlined.

Fig. 3 (case 3).—Large areas of caseous consolidation as well as fibrinous pleurisy in a lung.

The kidneys were normal in size. The capsules stripped easily. The kidney substance appeared normal.

The trachea and larynx were normal. There was some enlargement of the cervical lymph nodes, more marked on the right side. On section these were found to contain small abscesses, filled with grayish pus.

From the right axilla two large lymph nodes were removed. One was about 2 cm. in diameter. On section these were found to be partially necrotic.

The bone marrow of the femur was red and jelly-like. The vertebral bone marrow appeared normal.

Microscopic Examination: Sections from the heart were normal. Sections were made of bronchial and axillary lymph nodes. One section showed an enlarged node, with several abscess cavities present. These were filled with a grayish-yellow pus at autopsy. About the cavities there were areas of caseous necrosis and infiltration of the tissue with polymorphonuclear and epithelioid cells and other mononuclear cells. Scattered throughout the gland were numerous caseous areas. No giant cells were found. No tubercle bacilli or other bacteria were found in appropriately stained sections.

In some sections of the lungs marked caseous pneumonia was shown. In others the alveoli were distended with polymorphonuclear leukocytes. There was no interstitial pneumonia. About some of the caseous areas epithelioid cells were found, but there were no giant cells. Careful study failed to reveal any inclusion bodies. Various bacterial stains, including nile blue, failed to demonstrate B. tularensis, and no tubercle bacilli were found.

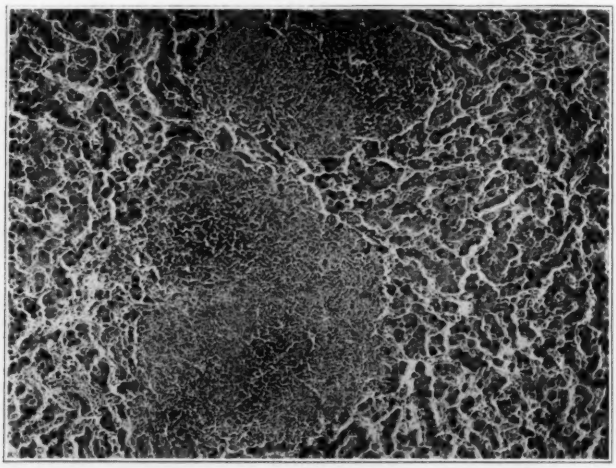

Fig. 4 (case 3).—Photomicrograph of the liver, showing areas of focal necrosis.

Scattered throughout the liver substance were numerous small caseous areas, not unlike tubercles. They had caseous centers with large epithelioid cells but no giant cells. These areas did not seem to bear any relation to the lobule, being both periportally and centrally located. Several of the periportal spaces showed a marked increase in lymphocytes. No bacteria were seen, and there were no acid-fast organisms present.

Scattered throughout the splenic pulp were numerous areas in various stages of caseation, with definite necrotic centers and a few large epithelioid cells scattered about. There were no giant cells.

A section taken through the back of the tongue and one of the tonsils showed some scarring of the tonsil. In one of the crypts there was a large caseous area similar to those seen elsewhere.

Bacteriologic Studies.—A culture of the heart blood was sterile. A culture of material from the lung showed Haemophilus influenzae and Pneumococcus (type I).

Anatomic Diagnosis.—The diagnosis was as follows: tularemia; caseous areas in the lungs, liver, spleen, lymph nodes and tonsils; diffuse caseous pneumonia; lobular pneumonia; fibrinopurulent pleurisy; an acute splenic tumor; a recent scar on the right thumb; an encapsulated foreign body in the lesser curvature of the stomach, and arteriosclerosis.

COMMENT

Of the three cases reported, the first seems to fall into the typhoid group, while the second and third are examples of the ulceroglandular form of tularemia, in the last two cases the portal of entry being an injury on the thumb. Perhaps a more inclusive term for all three would be the pulmonic form. It is conceivable that a local lesion was neglected in the first instance, since no suspicion of the true nature of the disease was held during the life of the patient. In the two cases in which a history of exposure was elicited, the source of infection was a wild rabbit, the usual offender. For this reason, as has been pointed out by Francis, the majority of tularemic infections are encountered in November, December and January. In this instance all three patients were admitted to the hospital in December.

The present series included one white woman, one white man and one Negro. All three were in the early fifties. (No particular significance is attached to this fact since tularemia has occurred in persons between the ages of 2 and 70.)

In case 2 the injury preceded the onset of symptoms by one week; in case 3, by only three days. The duration of the disease was almost the same in all three cases, death occurring on the twenty-fourth, twentieth and nineteenth days of the acute illness, respectively.

The clinical pictures were not dissimilar. The patients were acutely ill on admission. The course was characterized by sustained fever, tachycardia, dyspnea, prostration, delirium, signs of intoxication, cyanosis (sometimes out of proportion to the objective pulmonary signs and always extreme), constipation and abdominal distention. In each case at some period of the stay in the hospital it was deemed advisable to employ digitalis. The oxygen tent was frequently resorted to in all three cases.

Previous authors have stressed the ominous import of evidences of pulmonary involvement in cases of tularemia. Their claims are amply borne out in the present cases, in which the lungs were affected to a greater or lesser degree. Characteristically the signs were diffuse, terminally extensive but without indisputable signs of consolidation. In these respects they simulated the picture of postinfluenzal interstitial pneumonia, a clinical entity with which advanced tularemia might readily be confused.

In the only case in which the hemoglobin was determined more than once, rapidly progressive anemia was noted (from 90 per cent to

66 per cent within ten days). In another case the patient had persistent hemoglobinuria. This same patient acquired conjunctivitis, which was apparently unrelated to the chief malady. No significant cutaneous eruptions were noted, nor was there definite evidence of meningeal involvement.

So far as laboratory findings were significant, only agglutinations of blood and inoculations of animals provided definite information. The white blood cell count ranged between 3,500 and 18,000, the results of a majority of the determinations falling within normal or slightly elevated limits. Leukocytosis, when present, was of a polymorphonuclear type. Blood cultures on plain and dextrose agar gave uniformly negative results. Agglutinations for B. tularensis gave positive results in

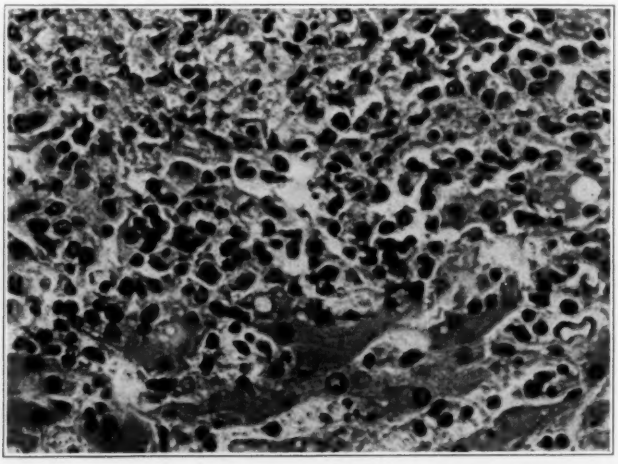

Fig. 5 (case 1).—Photomicrograph of the liver, showing the character of the cellular exudate at the periphery of a necrotic focus (× 400).

the two cases in which they were made; in case 2 there was a titer of 1:160 on the seventeenth day of illness; in case 3, a titer of 1:320 on the eighteenth day. None of the three serums agglutinated B. melitensis, a phenomenon which is met with in 25 per cent of cases of tularemia. Intraperitoneal injections of blood collected from the last two patients on the eighteenth and sixteenth days of the illness, respectively, brought about rapid death to guinea-pigs, at the autopsies of which there were found characteristic focal necroses in the liver and spleen.

The pathologic changes were strikingly uniform in the three cases. In all there was involvement of lymph nodes, lungs, liver and spleen. In the last case there were definite changes in the tonsillar crypts. The

lesion of tularemia resembles the soft tubercle in many ways but differs from it in two notable respects: the absence of tubercle bacilli and the absence of giant cells. In the less necrotic areas, the caseous nodules contain mononuclear cells and often a great many polymorphonuclears.

The pleurae in all instances were involved in an acute fibrinopurulent process, frequently with hemorrhages. In the lungs there were areas caused by caseous pneumonia, as well as many smaller necrotic lesions. The liver was enlarged and soft in consistency. The caseous nodules were distributed without apparent relation to the hepatic structure. Likewise the spleen was soft and usually enlarged. The lesions here were more abundant than in the liver. Scattered lymph nodes about the body were enlarged. The glands draining a primary lesion, in an

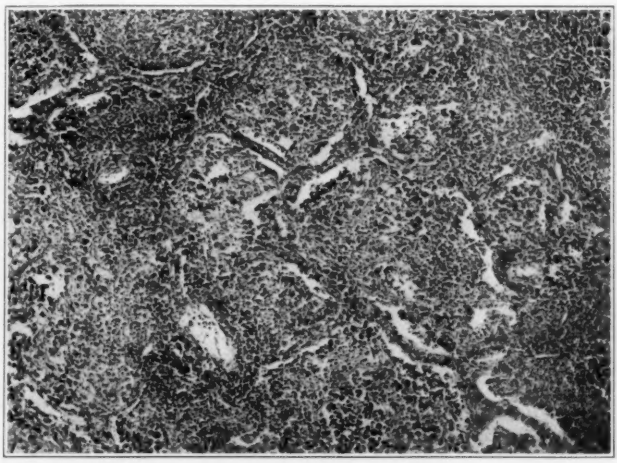

Fig 6 (case 2).—Photomicrograph of a lung, showing extensive pneumonia with destruction of the alveolar walls.

instance in which one was identified, tended to form coalescent caseous areas with beginning abscess production.

SUMMARY

Three cases of tularemia, two of which were diagnosed clinically and a third, pathologically, are reported.

The clinical course was characterized by sustained fever, tachycardia, dyspnea, prostration, delirium, signs of intoxication, extreme cyanosis, constipation and abdominal distention. In all three instances there was clinical evidence of pulmonary involvement.

At autopsy in each case, caseous nodules, usually small but sometimes in coalescent groups forming larger necrotic areas, were found in lymph nodes, the lungs, liver and spleen.

ACUTE, SUBACUTE AND CHRONIC ISOLATED MYOCARDITIS

REPORT OF A CASE

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AND
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Acute isolated myocarditis is a rare form of heart disease, first clearly described by Fiedler in 1889. In the American literature attention was first called to this entity in 1929 by Scott and Saphir [1] in their report of two cases. The latter paper contains bibliographic references to the thirty-six cases previously recorded. Search of the literature since 1929 reveals reports of at least ten other cases in which the histologic pictures correspond to that of acute isolated myocarditis (one each by Gallavardin and Gravier,[2] Legrand and Nayrac,[3] Mazzeo,[4] De La Chapelle and Graef,[5] Bailey and Andersen,[6] Boikan,[7] Bessem and Elsbach,[8] Maxwell and Barrett,[9] Miller [10] and Maslow and Lederer [11]). Boikan's case is described under the title "Myocarditis Perniciosa";

From the Departments of Pathology and Medicine of the City Hospital.

1. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, Am. Heart J. **5**:129 (Dec.) 1929.

2. Gallavardin, L., and Gravier, L.: Subacute Myocarditis with Interstitial Lesion; Case, Arch. d. mal. du coeur **22**:379 (June) 1929.

3. Legrand, R., and Nayrac, P.: Primary Interstitial Myocarditis of Anemic Origin, Compt. rend. Soc. de biol. **100**:886 (April 8) 1929.

4. Mazzeo, A.: Interstitial Myocarditis in a Child Two Years Old, Pediatria **37**:768 (July 15) 1929.

5. De La Chapelle, C. E., and Graef, I.: Acute Isolated Myocarditis with Report of a Case, Arch. Int. Med. **47**:942 (June) 1931.

6. Bailey, F. R., and Andersen, D. H.: Acute Interstitial Myocarditis, Am. Heart J. **6**:338 (Feb.) 1931.

7. Boikan, W. S.: Myocarditis Perniciosa, Virchows Arch. f. path. Anat. **282**:46, 1931.

8. Bessem, N., and Elsbach, E. M.: Isolated Acute Interstitial Myocarditis as Cause of Sudden Death, Geneesk. tijdschr. v. Nederl.-Indië **71**:1045 (Sept. 15) 1931.

9. Maxwell, E. S., and Barrett, C. C.: Acute Interstitial Myocarditis: Report of Case Following Severe Dermatitis Due to Sulphur Ointment, Arch. Dermat. & Syph. **29**:382 (March) 1934.

10. Miller, J.: Granulomatous Myocarditis, Canad. M. A. J. **29**:134 (Aug.) 1933.

11. Maslow, H. L., and Lederer, M.: Interstitial Myocarditis in Child Nineteen Months of Age, Am. J. Dis. Child. **45**:807 (April) 1933.

Miller's under the term "Granulomatous Myocarditis." An exact distinction between the advanced stages of myocarditis thus described and the various grades of change which may be noted in the myocardium in individual cases of isolated myocarditis is not possible with present knowledge.

Acute isolated myocarditis is characterized by a distinctive histologic picture. The myocardium shows a diffuse infiltration of the interstitial tissues by lymphocytes, mononuclear cells and, to a lesser degree, polymorphonuclear leukocytes, eosinophils and plasma cells. Numerous fibroblasts and new blood vessels may be seen. Occasionally small areas of necrosis are found in the muscle fibers themselves, but these are usually spared. The same heart may show a picture varying from that of cellular infiltration to those of the various stages of fibrosis. The endocardium and pericardium are usually not involved in the process, the lesion being entirely confined to the myocardium. The remainder of the body likewise shows no changes corresponding to the myocardial lesion, passive hyperemia and infarcts secondary to mural thrombi being the common findings.

Clinically, no distinctive picture exists by which the lesion may be diagnosed with any degree of assurance. Instances of sudden death without the previous occurrence of cardiac symptoms have been reported, as in Legrand and Nayrac's [3] 69 year old patient who died of rupture of the left ventricle four days after apparent recovery from a convulsive seizure. In a small number of cases the duration of illness extended from nine to twenty-one months, the picture in prolonged disease being one of severe congestive failure with all of the classic signs and symptoms. The usual course, however, is one of rapid and progressive myocardial insufficiency, the total illness frequently being measured in terms of weeks, with dyspnea, cyanosis, tachycardia and weakness as the outstanding symptoms. Thus, in the case of De La Chapelle and Graef,[5] only five weeks elapsed between the onset of cardiac symptoms (cough, shortness of breath, bloody sputum, edema) and death.

The condition has been described in both males and females; in the young and in the old. Of the recent cases Mazzeo's [4] was in a child aged 2 years; Maslow and Lederer's [11] in an infant of 18 months. The greatest number of cases appears between the ages of 20 and 50.

Examination of the heart itself usually yields negative results. The cardiac sounds have been described as being muffled, and occasional apical systolic murmurs have been heard. The significant physical findings are usually those of myocardial failure. The few electrocardiographic studies thus far recorded have been of little assistance in formulating a specific clinical diagnosis. Thus the electrocardiograms in the two cases of Scott and Saphir showed only left ventricular pre-

ponderance; that of De La Chapelle and Graef showed a prolonged PR interval, complete intraventricular block and low voltage in all leads with a normal sinus rhythm.

Accurate clinical diagnosis has also been rendered more difficult by the obscurity of the etiologic factors. Infection has most frequently been called the causal agent. In a few cases a history of rheumatic fever has been obtained. In others more or less remote infections (burns, gonorrhea, influenza, measles) have occurred, but a direct relationship between such infections and acute isolated myocarditis has not been established by either bacteriologic or histologic studies. In many cases neither a history of infection nor clinical evidence of its presence has been found.

REPORT OF A CASE

History.—J. M., a 23 year old white man, was first seen in the medical outpatient department of the City Hospital on March 20, 1934. The patient considered himself perfectly well until four weeks previously, when he noted shortness of breath and slight edema of the lower extremities. Prior to this time, according to the patient, he had been able to do hard manual labor. There was no history of acute rheumatic fever or of growing pains. No history of an infection could be obtained. Six months before, the patient had a severe rhinitis, from which he had recovered without complication. He said that he had not had gonorrhea or syphilis. There was no history of contact with tuberculosis.

Examinations.—The patient revealed cyanosis of the face and neck, distention of the jugular veins and a few râles at the bases of the lungs. He was moderately short of breath. There was increased precordial activity, the apex being in the sixth intercostal space in the anterior axillary line. The heart sounds were distant; there were no murmurs. A tender liver was palpable 1 fingerbreadth below the right costal margin. There was slight peripheral edema. The temperature was 37 C. (98.6 F.); the pulse rate was 112; the blood pressure was 110 systolic and 75 diastolic. Digitalis and rest in bed afforded no relief.

The patient was again seen in the clinic on March 27, presenting the same picture. Fluoroscopic examination and an x-ray film of the heart showed an enlargement of the cardiac shadow mainly in the left ventricular region. The aortic knob was effaced, and there was bulging in the region of the pulmonary artery and left auricle. The right side of the diaphragm was slightly elevated. The pulmonary fields were clear. There was no pathologic process in the mediastinum. The patient finally consented to enter the hospital on the evening of March 31.

On admission dyspnea and cyanosis were marked, and the patient was most uncomfortable. Examination of the eyegrounds showed them to be entirely normal. There was moderate jugular distention. Both lungs were filled with numerous coarse râles. The liver could be palpated 2 fingerbreadths below the right costal margin and was tender. There was slight pitting edema of the feet and ankles. The peripheral vessels were not sclerotic. There was no pulsus paradoxus. The femoral vessels were palpable.

Examination of the heart revealed findings similar to those already noted. The sounds appeared distant, and there was a short, soft, systolic murmur at the apex. The blood pressure was 90 systolic and 70 diastolic. The blood showed 5,150,000 red and 35,200 white cells per cubic millimeter, and 90 per cent hemo-

globin (Sahli). The Wassermann reaction of the blood was negative. The urea nitrogen was 49.1 mg., creatinine 3.8 mg., and sugar 64.3 mg., per hundred cubic centimeters. The urine contained albumin (2 plus). Sugar was not present. There were many hyaline and granular casts, many white blood cells and occasionally red blood cells.

Course.—The patient showed considerable improvement following venesection, intranasal administration of oxygen, and use of morphine and atropine in small doses. He was fairly comfortable during the night and the next morning, although no significant change in the physical signs was evident. Death occurred rather

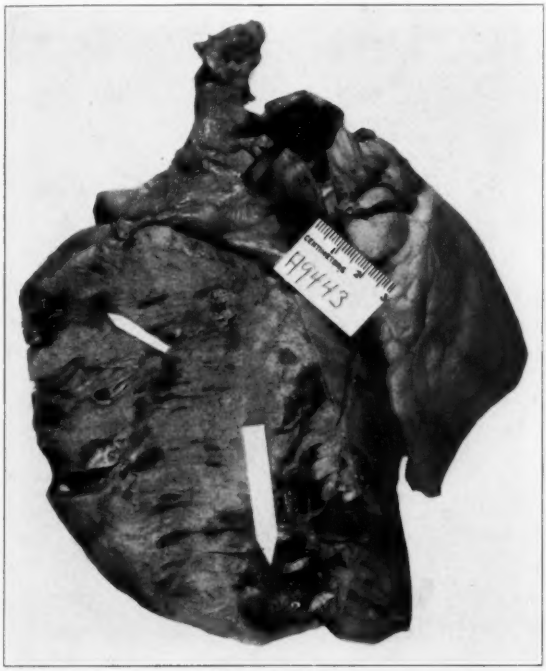

Fig. 1.—A tangential section through the wall of the left ventricle to show the extent of myocardial damage. The upper arrow points to the type of lesion in the myocardium. The lower arrow points to a mural thrombus in the wall of the left ventricle.

suddenly about twenty hours after admission to the hospital and five and a half weeks after the onset of illness. The temperature was 37 C. (98.6 F.) until shortly before death, when it rose to 38.2 C. (100.7 F.). The pulse rate varied between 80 and 100 and the respirations between 24 and 30. No electrocardiogram was obtained. The clinical diagnosis submitted was: cardiac hypertrophy and dilatation, with myocardial insufficiency—etiology undetermined.

Autopsy.—The body was well developed and exceedingly well nourished. It measured 180 cm. in length and weighed approximately 91 Kg. There was con-

siderable cyanosis of the face and neck. The peritoneal cavity contained 200 cc. of clear straw-colored fluid, the right pleural cavity 1,000 cc., the left pleural cavity 200 cc. and the pericardial sac 170 cc. On the posterior aspect of the right auricle a few fine fibrinous strands were seen on the epicardium. The heart as seen in situ was a peculiar yellowish pink and exceedingly flabby.

The heart weighed 450 Gm. The shape was somewhat distorted by the fact that all the chambers were dilated and filled with fresh blood clot and the heart flabby. The epicardial surface was everywhere thin, smooth and glistening, except on the posterior aspect where small irregular depressed areas were present, over which a small amount of fibrin was seen. When the heart was viewed externally, a number of oblong depressed purple soft areas on the anterior and posterior surfaces of the heart were present. The interior of the auricles was not remarkable. All the valve leaflets were thin, smooth and pliable and showed no gross pathologic changes. Both ventricles showed distinct flattening of the columnae carneae; their chambers were slightly enlarged, and through the endocardium could be seen depressed oblong violaceous areas similar to those seen on the outer surface.

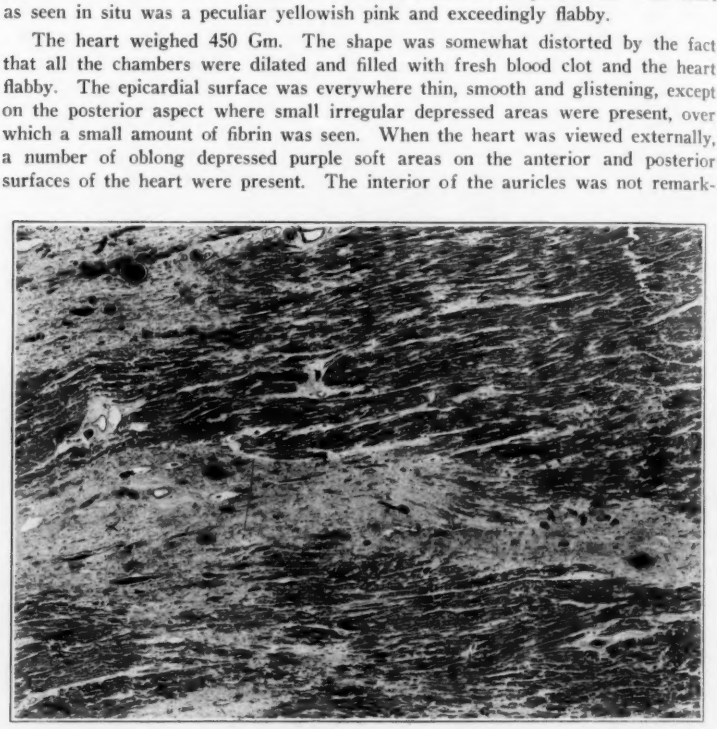

Fig. 2.—Relatively old areas of fibrous connective tissue in the myocardium. Hematoxylin and eosin; × 25.

Many sections through the myocardium revealed a peculiar mottled pinkish-yellow discoloration. Section through the violaceous areas showed that they were poorly demarcated and of distinctly gelatinous appearance. In the apex of both the right and the left ventricle an organizing mural thrombus was found densely adherent to the myocardium and enmeshed in the interstices of the columnae carneae. The coronary arteries were carefully explored and revealed the usual caliber with thin smooth intimal surfaces without thrombus or embolus.

The lungs showed edema and passive hyperemia. No infarcts were present.

The kidneys and the spleen showed passive hyperemia and recent infarcts. A few of the veins about the prostate showed thrombosis, but careful search through all the organs failed to reveal any focus of suppuration or infection. The rest of the veins showed only passive hyperemia. The postmortem culture of blood from the heart was sterile; the autopsy had been performed fourteen and one-half hours after death. Permission for removal of the brain was not obtained.

Microscopic Examination.—Many sections of the myocardium showed inflammation, variable as to degree and character. The inflammation was essentially interstitial and diffuse, although focal areas of inflammation were not infrequently present. In the diffuse areas of inflammation there was an abundant infiltration by plasma cells, lymphocytes and polymorphonuclear leukocytes, and many of the latter type were eosinophils. In some places the inflammatory change was more

Fig. 3.—An area of acute and subacute inflammation with destruction of myocardial fibers and disorganization of architecture.

acute and the polymorphonuclear leukocytes were more numerous, whereas in other situations acellular fibrous scars replacing muscle fibers were not infrequent. In some areas there was actual granulation tissue present with new capillary formation and fibroblastic proliferation. The majority of the lesions were found in perivascular situations, although many were isolated in the myocardium remote from vessels. The inflammatory reaction invaded and destroyed the myocardial fibers, and many showed a granular type of necrosis. Extensive necrosis was absent, and no giant cells were present. The epicardium overlying areas of acute inflammation showed a deposition of fibrin on the outer surface. In none of the sections studied did the appearance of the exudate suggest rheumatic fever. Nothing that can be interpreted as Aschoff bodies was seen. The vessels were not remarkable. Sections stained by the Ziehl-Neelsen and Gram methods failed to reveal the presence of organisms.

COMMENT

The clinical picture in this case was unusual because of the progressive and rapid myocardial failure in a young man without apparent cause. The patient's age made the diagnosis of coronary sclerosis doubtful. Neither the history nor the physical findings indicated a congenital cardiac lesion or an organic valvular lesion. Acute pericarditis and pericardial effusion could not be substantiated from physical signs and the previous fluoroscopic examination. The lack of any evidence in the history or clinical examination of acute infection antedating the present illness tended to rule out the usual picture of acute myocarditis secondary to infection. The most likely possibility appeared to be some unusual form of rheumatic myocarditis. However, the lack of a history of rheumatic infection, the inability to demonstrate pericardial involvement or a valvular lesion, the absence of fever, the ability of the patient to be up and around until his admission to the hospital rendered it unlikely that rheumatic fever was the cause. The clinical diagnosis submitted recognized the impossibility of ascribing, with any degree of certainty, a causative agent to explain a cardiac lesion so severe that but five and one-half weeks elapsed between apparent health and death.

Because it is a rare disease and because pathognomonic signs of its presence are yet to be described, the clinical recognition of acute isolated myocarditis rests, perhaps, on diagnosis by exclusion. In some cases the history only is characteristic. Therefore, in any young person with a history of rapid and progressive myocardial failure the exclusion of the ordinary etiologic factors, especially rheumatic fever, should always lead to the consideration of acute isolated myocarditis as the clinical diagnosis.

The extent of damage to the myocardium is both grossly and microscopically severe and explains perhaps the short duration. Old fibrous scars are present which must have antedated the onset of symptoms. These scars are probably inflammatory in origin, since vascular changes are not present. The apparent difference in the age of the changes suggests that, whatever the etiologic agent, it had been operating for a considerable period of time—until the functional mass of muscle was reduced below the level necessary for life. It is probable that this inflammatory process was present and subclinical in its manifestations for some time before the patient died. There is nothing in the microscopic appearance of the myocardial lesions to suggest a specific granuloma. Careful search also failed to reveal the changes associated with rheumatic myocarditis, in the myocardium, endocardium, valves or vessels. The thrombosis seen in the periprostatic venous plexus was secondary to the failing circulation and showed no gross or microscopic evidence of infection.

CANCER AS A PROBLEM IN METABOLISM

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NEW ORLEANS

Cancer has taken an enormous toll of human lives for the last three thousand years. It is only within the last thirty-five years that this disease has been studied from the experimental point of view. Woglom,[1] in the annual Gross lecture of the Philadelphia Pathologic Society in 1931, divided the latter period into three decades. In the first decade the limits within which malignant tumors can be transplanted were determined; a method of protecting against their inoculation was found; the resistance of the cancer cell to various agents was compared; its cultivation in vitro was begun; the hereditary nature of cancer in mice was predicated, and a transmissible sarcoma of the fowl was discovered. In the second decade the rate of growth of the cancer cell was determined, and two methods of producing tumors experimentally were discovered. In the third decade another method of inciting the growth of tumors was reported; the chemical nature of the carcinogenic hydrocarbons in tar was established; the amount of irritation necessary to initiate neoplasia was determined, and the age at which cancer is most frequent was established.

In the present, fourth, decade, even though it has not yet passed, much experimental work has been done on the metabolism of the cancer cell and on endocrine imbalance as a cause of tumors. I wish to outline some of this newer work. No attempt will be made to review all the published experimental evidence, but enough will be given to show that these newer points of view are proving to be of unusual importance to the understanding of the nature of the malignant process.

CARBOHYDRATE METABOLISM OF TUMORS

Warburg[2] and his co-workers began their first experiments on the metabolism of tumors in 1924. Since then similar studies have been

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From the Department of Biochemistry, Louisiana State University Medical Center.

Read, in summary, before the Faculty Club of the Medical Center, Dec. 11, 1934, and before the members of the Eclat Club on their visit to New Orleans, Dec. 14, 1934.

1. Woglom, W. H.: Experimental Cancer Research, Am. J. M. Sc. **181**:157, 1931.

2. Warburg, O.: The Metabolism of Tumors, translated by Frank Dickens, New York, R. R. Smith, Inc., 1931.

carried out in many parts of the world. Figure 1 shows the Warburg manometric apparatus.

The tissues the respiration of which is to be determined are placed in the outer portion of the respiration bottle in a respiration medium of isotonic saline, Locke's or Ringer's solution. Potassium hydroxide is placed in the central compartment. The system is then washed out with oxygen, the stoppers and stop-cocks are closed, and the bottle is placed in a bath maintained constantly at 37 C. and is shaken

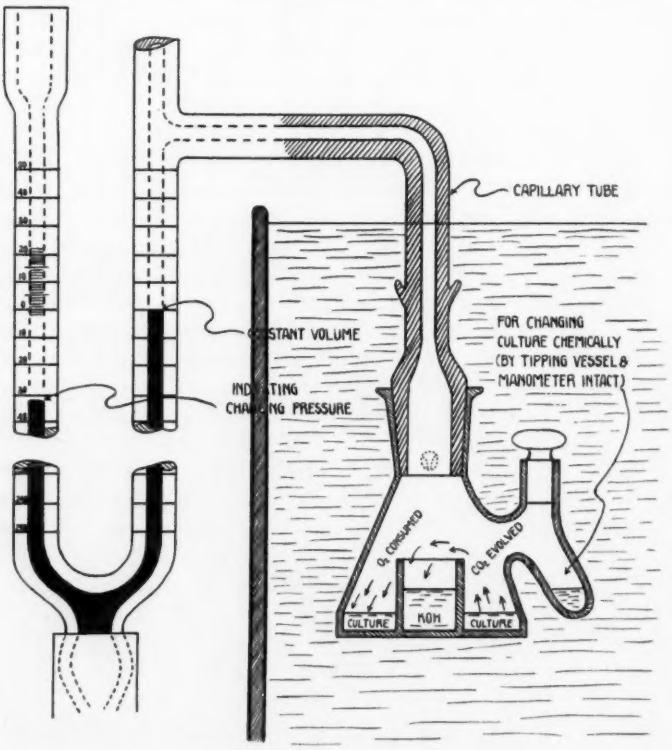
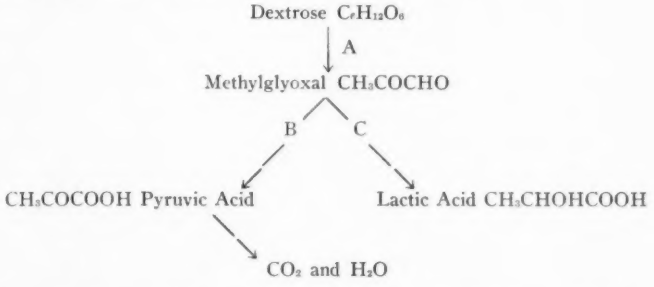


Fig. 1.—The Warburg manometric apparatus.

for stated lengths of time. As tissue respiration occurs, oxygen is consumed and carbon dioxide is evolved, which is absorbed by the alkali in the central compartment. The lowering of the pressure through the consumption of oxygen is measured on the manometer, which makes possible an accurate calculation of the oxygen consumed by the tissue.

Warburg showed that in tumor tissue in the absence of oxygen from ten to twenty times as much lactic acid is formed as in normal tissue. This excess glycolysis is not absolutely specific for tumor

tissue, since it is also found in brain and retina. Nevertheless, it is certain that the disturbance in tumor cells consists in their incapability of increasing oxidation in the same degree as glycolysis. Dickens and Simer [3] showed the difference in the carbohydrate metabolism of normal and neoplastic tissues by the accompanying scheme.



The deficient oxidation of tumor tissue is thus accounted for by a break in the oxidative route B between methylglyoxal and pyruvic acid with an increased glycolysis along route C. As Warburg expressed it, "Interference with the respiration of a growing cell is, from the standpoint of the physiology of metabolism, the cause of tumors. If the respiration of a growing cell is disturbed, as a rule the cell dies. If it does not die a tumor cell results. This is no theory, but a comprehensive summary of all the measurements at present available."

Warburg's work has been confirmed by a number of investigators: Dickens,[4] Dodds,[5] Glover,[6] Fischer-Wasels [7] and others. Working with benign and malignant tumors of man, Glover found an exact correlation between the histologic malignancy and the anaerobic glycolysis. Boyland [8] recently reviewed the work on the biochemistry of malignant tissue, and Dodds [9] and Dickens,[4] that on the carbohydrate metabolism.

3. Dickens, F., and Simer, F.: A Note on the Metabolism of Tumors, Lancet **2**:10, 1930.

4. Dickens, F.: Cancer as a Problem in Tissue Metabolism, Cancer Rev. **6**: 57, 1931.

5. Dodds, E. C.: Recent Biochemical Research with Special Reference to the Normal and Malignant Cell, Am. J. Cancer **15**:2765, 1931.

6. Glover, E. C.: The Metabolism of Human Tumors, Am. J. Cancer **15**: 1043, 1931.

7. Fischer-Wasels, B.: General Predisposition to Tumor Formation, Wien. klin. Wchnschr. **44**:629, 1931.

8. Boyland, E.: The Biochemistry of Malignant Tissue, Ann. Rev. Biochemistry **3**:400, 1934.

9. Dodds,[5] p. 2765.

10. Footnote deleted by the author.

LIPOID METABOLISM AND CHOLESTEROL; IRRADIATION AND CARCINOMA OF THE SKIN

Numerous workers have shown that there is an increase in both cell lipids and cell cholesterol in benign and malignant tumors (Yasuda and Bloor,[11] Roffo,[12] Roffo and Thomas,[13] Burgheim and Joel,[14] Marqués,[15] Kirgreen,[16] Willheim and Fuchs,[17] Uramoto,[18] Brikker and Lasaris,[19] LeMay,[20] Jowett,[21] Schaaf and Werner[22] Tesauro[23] and others). Roffo,[13] in his monograph, "La chimie du cancer," summarized the metabolic aspects of the cancer cell, together with the rôles played by lecithin, cholesterol and lipoids. It seems reasonable to believe that the cancer cell may utilize fat as a source of energy for its rapid growth. These studies of the cholesterol content of tumors are of much importance in cases of cancer of the skin.

Further work by Roffo[24] is interesting in this connection. He stated that the skin is more frequently attacked by cancer than any other

11. Yasuda, M., and Bloor, W. R.: Lipin Content of Tumors, J. Clin. Investigation **11**:677, 1932.

12. Roffo, A. H.: Heliotropism of Cholesterol in Relation to Skin Cancer, Am. J. Cancer **17**:42, 1933.

13. Roffo, A. H., and Thomas, J.: La chimie du cancer, Paris, Vigot Frères, 1933, pp. 110 and 120.

14. Burgheim, F., and Joel, W.: On the Relation Between Cancer and Lipoid Metabolism, Klin. Wchnschr. **10**:397, 1931.

15. Marqués, E. J.: The Action of Radiations on Cholesterol, Néoplasmes **12**:159, 1933.

16. Kirgreen, O.: Cholesterol Metabolism in Cancer Patients, Arch. f. klin. Chir. **177**:383, 1933.

17. Willheim, R., and Fuchs, G.: The Cholesterol Content of the Cancer Lipoids, Biochem. Ztschr. **247**:297, 1932.

18. Uramoto, M.: Studies on the Changes in the Amount of Cholesterol and Phosphorous Compounds of Cancerous Tissue at the Various Periods of Its Growth, J. Biochem. (Japan) **16**:69, 1932.

19. Brikker, F., and Lasaris, J.: The Lipoid Content of Cancer Tissue, Ztschr. f. Krebsforsch. **37**:432, 1932.

20. LeMay, P.: Lipoids and Cancer, Néoplasmes **10**:158, 1931.

21. Jowett, M.: The Phosphatide and Cholesterol Content of Normal and Malignant Human Tissues, Biochem. J. **25**:1991, 1931.

22. Schaaf, F., and Werner, A. J.: The Relation of Cholesterol, Phosphatide and Total Fat Content of the Blood to the Origin of Xanthoma, Arch. f. Dermat. u. Syph. **162**:217, 1930.

23. Tesauro, G.: The Influence of Lipids upon Tumor Growth, Ztschr. f. Krebsforsch. **35**:269, 1932.

24. (*a*) Roffo, A. H.: Cancer y sol: El desarrollo experimental de tumores espontaneos por las irradiaciones ultravioletas en relacion con el heliotropismo de la colesterina, Bol. Inst. de med. exper. para el estud. y trat. del cáncer **10**:417, 1933. (*b*) Roffo.[12]

organ of the body. Table 1 gives the incidence of carcinoma in different parts of the face in 2,000 patients examined at the Buenos Aires Cancer Institute. About the same frequencies were observed by Nielsen [25] in 1,000 patients with skin cancer in the Radium Station in Copenhagen. In the Negro, in whom pigmentation of the skin prevents absorption of light, carcinoma of the skin, according to Roffo, is rare.[26] He showed that rat and human tumors may contain more than twice the normal concentration of cholesterol (fig. 2), and that it is possible, by keeping animals on a cholesterol-free diet, to modify the soil in such a way as to inhibit or prevent the growth of tumors. He expressed the belief that exogenous dietary factors and pregnancy are also responsible for the increased cholesterol content of the blood and precancerous growths. The large amount of cholesterol in the skin of the face is due, according to Roffo, to the exposure of the face to sunlight. The cholesterol concentration in the skin of the face is two or three times that in the skin of the abdomen, which is usually protected from the sun by clothing.

TABLE 1.—*Cancer of the Face*

	Per Cent
Nose	61.4
Cheek	18.0
Ear	7.9
Forehead	7.7
Temporal region	4.0

Roffo [27] showed that while ultraviolet rays of wavelengths from 3,900 to 2,300 angstroms exerted no inhibition on the growth of the fibroblasts of chicken heart or rat sarcoma, the luminous rays of wave-

25. Nielsen, J.: Cancer of the Skin, Ugesk. f. læger **95**:464, 1933.

26. Dr. J. K. Howles, in a recent survey of 1,987 cases of epithelioma of the skin observed at Charity Hospital in New Orleans over a period of twenty-seven years, gave its incidence among the white and colored races as follows:

Site	Cases	Racial Distribution	
		White	Colored
Cheek	616	598	18
Lips	488	468	20
Nose	360	354	6
Ears	126	123	3
Neck	91	89	2
Forehead	125	124	1
Eyes	88	85	3
Chin	44	41	3
Mouth	49	41	8

27. Roffo, A. H.: Comparison of Luminous and Ultraviolet Rays on Growth of Normal and Neoplastic Cells in Tissue Culture, Bol. Inst. de med. exper. para el estud. y trat. del cáncer **10**:209, 1933.

lengths from 7,000 to 3,900 angstroms inhibited the growth of the fibroblasts of chicken heart in four hours and of those of sarcoma in two hours.

Correa [28] summed up Roffo's views on the relationship of cholesterol to cancer as follows:

Cholesterol seems to be the substance which acts in preponderant form: Though it has not yet been possible to establish exactly the relation of cause to effect, the evidence accumulated by Professor Roffo seems to ascribe to cholesterol a positive position in the preparation of the soil and consequently in the genesis and evolution of malignant tumors. This evidence is as follows:

1. The cholesterol increase in neoplastic tissue, blood and cholesterologenous organs

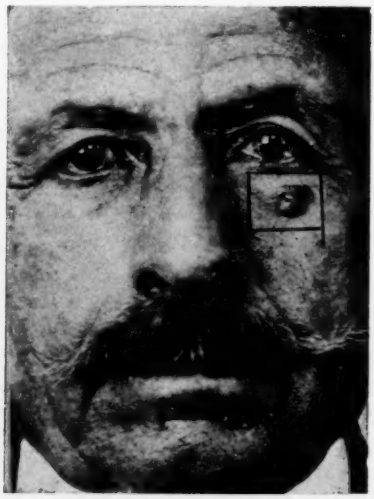


Fig. 2.—A precancerous lesion of the face. The cholesterol content of tissue from the area indicated was 1.1 Gm. per hundred grams of tissue; that of normal skin is 0.49 Gm. per hundred grams of tissue. (Courtesy of Prof. A. H. Roffo.)

2. The absorption of cholesterol by malignant tumors, shown in vivo and in vitro
3. The cholesterol contents according to age, and the relation between the maximum content and the frequency of tumors
4. Its presence in precancerous stages
5. The photo-active function and the deposits of cholesterol in parts of the skin exposed to the sun
6. The localization of skin tumors in these parts

28. Correa, L. M.: Los lípidos en el cáncer: Investigaciones efectuadas en el Instituto de Medicina Experimental, Bol. Inst. de med. exper. para el estud. y trat. del cáncer **10**:511, 1933.

Roffo [24a] recently subjected rats to ultraviolet radiation, beginning with a daily five minute exposure, which was gradually increased to one of twenty hours. The latter was given daily for from six to eight months. Tumors on the eyes, ears and back of the head were produced (fig. 3). Herlitz, Jundell and Wahlgren,[29] Findlay [30] and Putschar and Holtz [31] also produced malignant growths in rats and other animals by irradiation. These observations are being confirmed by me.

Mandel [32] showed that irradiation of the ovaries of rats from 7 to 10 days of age was followed by precocious opening of the vagina and estral changes at approximately 22 days of age. The irradiated ovaries at this time revealed huge follicles with enormous antrums. The roentgen treatment greatly stimulated the growth of the follicles, which then became functionally hyperactive. These results, together with

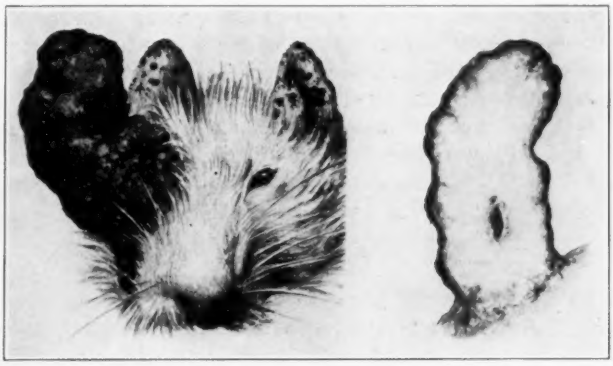


Fig. 3.—Tumor of the eye of a rat caused by exposure to ultraviolet rays in increasing amounts over a long period of time. (Courtesy of Prof. A. H. Roffo.)

those mentioned in the foregoing paragraph, show that prolonged irradiation may produce cancerous changes while moderate doses may cause estral changes. Dodds [33] showed that either irradiation or vitamin D can produce estral changes.

29. Herlitz, C. W.; Jundell, I., and Wahlgren, F.: Weitere Untersuchungen über die Wirkung einiger Sterine und des ultravioletten Lichtes auf weisse Mäuse, Acta pædiat. **12**:221, 1932.

30. Findlay, G. M.: Cutaneous Papillomata in the Rat Following Exposure to Ultraviolet Light, Lancet **1**:1229, 1930.

31. Putschar, W., and Holtz, E.: The Production of Carcinoma of the Skin in Rats by Long Continued Ultraviolet Irradiation, Ztschr. f. Krebsforsch. **33**:219, 1931.

32. Mandel, J.: Ovarian Irradiation and Sexual Precocity in the Rat, Proc. Soc. Exper. Biol. & Med. **32**:155, 1924.

33. Dodds, E. C.: The Hormones and Their Chemical Relations, Lancet **1**:987, 1934.

Sumi and Nakahara [34] found that the absorption bands of 10 per cent aqueous extracts of four types of tumors (Rous chicken sarcoma, Fujinawa rat sarcoma, Flexner-Jobling rat carcinoma and Bashford mouse carcinoma), measured with the Hilger quartz spectrograph, type E-6, extended from 3,000 to 2,500 angstrom units with the center at 2,700 angstrom units. The intensity of absorption seemed greater in rat carcinoma, but this and mouse carcinoma showed much stronger absorption than did chicken sarcoma.

Gurwitch [35] of Leningrad, addressing the International Congress on Cancer in Madrid in 1933, stated that malignant tissue, as well as any aggregation of proliferating cells, can give off ultraviolet radiations, which can then induce mitosis. This was shown as follows: A quartz spectrograph which had a scale of wavelengths instead of a photographic plate was placed between a tumor and a yeast culture. The tumor was placed in front of the slit of the spectrograph, and a series of yeast cultures was placed in front of the different divisions on the spectrographic scale. Stimulation occurred at some wavelengths but not at others. He stated that the emission of ultraviolet rays occurs as the result of many chemical reactions. Only the blood, nerves, muscles and small intestine were found capable of emitting the rays.

Matsuzki [36] recently showed that the intensity of ultraviolet absorption is greater in rat sarcoma than in rat carcinoma.

THE CARCINOGENIC HYDROCARBONS

Dodds,[33] in his second Goulstonian lecture, delivered before the Royal College of Physicians at London on March 8, 1934, discussed the recent work on the carcinogenic hydrocarbons and their relation to the female sex hormone, estrin.

Yamagiwa and Ichikawa [37] first showed, in 1915, that tar painting produced cancer in rabbits. This significant observation has stimulated an immense amount of work on the subject of tar cancers. Woglom [38] reviewed 290 papers on this subject published previous to the end of 1926, and Seelig and Cooper [39] listed 391 in 1933. The most recent work in this connection has been reported by Dodds.[33]

34. Sumi, M., and Nakahara, W.: Ultraviolet Absorption Spectra of Tumor Extracts, Especially of Rous Chicken Sarcoma, Gann **26**:175, 1932.

35. Gurwitch: Foreign Letters, J. A. M. A. **102**:386 (Feb. 3) 1934.

36. Matsuzki, I.: Spectrographic Pathological Studies of Malignant Tumors, Tr. Jap. Path. Soc. **23**:719, 1933.

37. Yamagiwa and Ichikawa: Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **15**:295, 1915; **17**:19, 1917; **19**:483, 1918.

38. Woglom, W. H.: Experimental Tar Cancer, Arch. Path. **2**:532 (Oct.) 1926.

39. Seelig, M. G., and Cooper, Z. K.: A Review of the Recent Literature of Tar Cancer, Am. J. Cancer **17**:589, 1933.

At first it was thought that the tar produced a chronic irritation which later prepared the tissue for a malignant change. But not all tars will produce cancer when painted on the skin. The observations of Kennaway,[40] of Cook, Hieger, Kennaway and Mayneord,[41a] of Cook [41b] and of Cook, Hewett and Hieger [41c] in England are very important in this connection. Kennaway showed that by heating isoprene or acetylene in the presence of hydrogen a carcinogenic agent could be produced which contained only carbon and hydrogen. In 1927 Mayneord studied the spectra of such synthetic mixtures and observed their similarity to the spectrum of the carcinogenic tar. Hieger, also, had observed the resemblance between the fluorescence spectrum of benzanthracene and a carcinogenic coal tar. Benzanthracene, however, is only weakly carcinogenic.

Clar [42] had previously synthesized di-benzanthracene, which gave 58 cancers and 9 papillomas in 190 mice, of which only 140 lived more than six months. Benzanthracene consists of four benzene rings, while di-benzanthracene adds one more benzene ring in a certain position. Tumors have been produced in similar fashion in fowls by Burrows [43] and Peacock.[44] Lacassagne [45] injected a solution of 1, 2, 5, 6-di-benzanthracene into the testicle of a rabbit; at the site of the injection a malignant epithelial tumor appeared which produced numerous metastases in the lungs. Cook and co-workers [41] then showed that a group of compounds chemically related to 1:2—benzanthracene were carcinogenic when applied to animals.

Figure 4 shows the structural chemical relationship between the bile acids, the male and female sex hormones, cholesterol, ergosterol, calciferol (vitamin D) and the carcinogenic hydrocarbons. Somewhat

40. Kennaway, E. L.: The Formation of a Cancer Producing Substance from Isoprene, J. Path. & Bact. **27**:233, 1924; Experiments upon Cancer Producing Substances, Brit. M. J. **2**:1, 1925; Further Experiments upon Cancer Producing Substances, Biochem. J. **24**:497, 1930.

41. (*a*) Cook, J. W.; Hieger, I.; Kennaway, E. L., and Mayneord, W. V.: The Production of Cancer by Pure Hydrocarbons, Proc. Roy. Soc., London, s.B **111**:455, 1932. (*b*) Cook, J. W.: The Production of Cancer by Pure Hydrocarbons, ibid. **111**:485, 1932. (*c*) Cook, J. W.; Hewett, C. L., and Hieger, I.: Coal Tar Constituents and Cancer, Nature **130**:926, 1932.

42. Clar, E.: Zur Kenntnismehrkernigen aromatischer Kohlenwasserstoffe und ihrer Abkömmlinge: I. Mitteilung Dibenzanthracen und ihre Chinone, Ber. d. deutsch. chem. Gesellsch. **62** B:350, 1929.

43. Burrows, H.: A Spindle-Celled Tumor in a Fowl Following Injection of 1:2:5:6 Di-Benzanthracene in a Fatty Medium, Am. J. Cancer **17**:1, 1933.

44. Peacock, P. R.: Production of Tumors in Fowls by Carcinogenic Agents, J. Path. & Bact. **36**:141, 1933.

45. Lacassagne, A.: Essais de production de cancer chez le lapin au moyen du 1-2-5-6, dibenzanthracène, Compt. rend. Soc. de biol. **114**:660, 1933.

the same structure has also been given for the cardiac aglucones by Jacobs and Elderfield [46] and Tschesche.[47]

The extensive researches of the English workers referred to have shown that these carcinogenic hydrocarbons may be formed from the naturally occurring bile acids [48] and sterols by the chemical reactions of reduction, dehydration and dehydrogenation. They might also arise from the degradation products of the sterols in the body.

According to Dodds, 1:2 benzpyrene will produce cancer in about half the time that is required by 1, 2, 5, 6-di-benzanthracene. This finding has been confirmed by Maisin and Liégois [49] and by Sonnie and Truhaut.[50] It is therefore the most active carcinogenic agent known. The phenanthrene ring type of compound has recently been shown to be a normal constituent of the body. By taking the absorption spectrum with a sn.all quartz spectrograph, it will be possible to detect these carcinogenic agents in tar and oils and thus protect industrial employees against them.

Another line of investigation has shown that the compounds of the closely related phenanthrene group are capable of causing estrus in small castrated animals. Cook and Dodds [51] observed full estrus

46. Jacobs, W. A., and Elderfield, R. C.: The Structure of the Cardiac Aglucones, Science **80**:533, 1934.

47. Tschesche, R.: Angewandte Chem. **47**:729, 1934.

48. Sellards (Ulceration of the Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of Bile Salts, Arch. Int. Med. **4**:502 [Nov.] 1909) and Tashiro and co-workers (M. Bull. Univ. Cincinnati **6**:110, 124, 130, 134 and 144, 1931) observed the development of gastric ulcers in guinea-pigs following intraperitoneal injection of bile salts. These important results have been confirmed by Anderson and Farmer (Development of Gastric Ulcers and Decrease in Reducing Power of Adrenals Following Injection of Bile Salts, Proc. Soc. Exper. Biol. & Med. **32**:31, 1934), who stated: "We injected approximately 40 guinea pigs with varying amounts of bile salts (Fairchilds). The expected individual variations in susceptibility were observed, but injections of 0.1 gm. or more generally caused death and extensive ulceration of the gastric mucosa. The latter was usually so marked that the site of the ulcers could be plainly observed from the outer surface of the stomach, appearing as thin, semi-transparent areas. In three animals perforation occurred, gastric contents being found in the peritoneal cavity at autopsy." In view of the fact that a gastric ulcer may later develop into gastric cancer, the foregoing findings are of interest at this time.

According to Science (Science [suppl.] **80**:14 [Dec. 28] 1934), Dr. Cook and associates at the London Free Cancer Hospital have recently transformed, by simple chemical means, a naturally occurring bile acid into a cancer-producing substance.

49. Maisin, J., and Liégois, P.: Carcinogenicity of Benzpyrene, Compt. rend. Soc. de biol. **115**:733, 1934.

50. Sonnie, C., and Truhaut, C.: Carcinogenic Chemicals, Bull. Assoc. franç. p. l'étude du cancer **23**:6, 1934.

51. Cook, J. W., and Dodds, E. C.: Sex Hormones and Cancer Producing Compounds, Nature **131**:205, 1933.

when 100 mg. of 1:2 benzpyrene or 5:6:cyclopenteno-1:2:benzanthracene was injected. However, these compounds are much more carcinogenic than estrogenic. According to Dodds, di-benzanthracene is carcinogenic in the aromatic state and estrogenic when suitably hydrogenated and supplied with hydroxyl groups.

ENDOCRINE IMBALANCE IN THE PATHOGENESIS OF SOME TYPES OF CANCER

Schoonover [52] in 1931 discussed the changing attitude toward cancer, stressing the importance of studies of cell physiology and cell chemistry

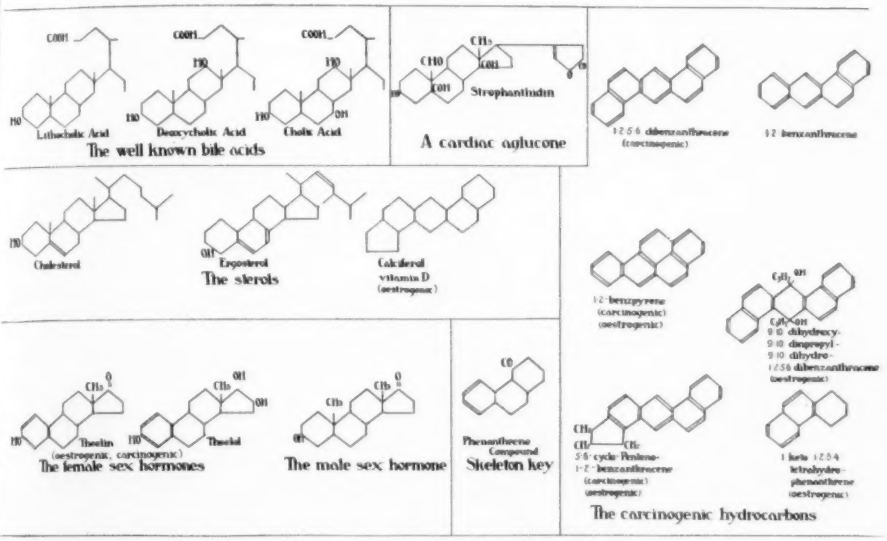


Fig. 4.—Chart showing the chemical structural relationship between the bile acids, sterols, sex hormones and carcinogenic hydrocarbons.

in this connection. He concluded that studies of cell physiology indicate that cancer is a phenomenon of normal cells which have grouped themselves into masses, typical of tumors, because of the presence of a chemical substance. This substance is present in tar, paraffin, soot, certain chemicals, the products of chronic inflammation and possibly certain foods. Endocrine imbalance as a cause of certain types of cancer has been suggested by a number of workers.

52. Schoonover, F.: The Changing Attitude Towards Cancer, Texas State M. J. **26**:806, 1931.

The rapid growth of some tissues is evidently associated with the activity of the glands of internal secretion, especially with that of the thymus. The increase in size of the mammary glands at puberty and their enlargement during pregnancy, the growth of the antlers of the deer during the rutting season and the enormous growth of the reproductive organs of the salmon at the expense of their muscle tissue during the spawning season are cases in point.

Since Sugiura and Benedict [53] have published 137 references to work on the hormones in cancer, I shall list only the more important of them here. The very important advances that have recently been made in the isolation of different endocrine products and the discovery of their remarkable physiologic effects naturally lead one to speculate on the effect of these hormones in malignant conditions. For instance, Allen and Doisy [54] showed clearly that estrin is capable of producing the most extensive cell growth and proliferation of tissue. When injected into immature female animals it will, in the short space of two days, bring on the physiologic phenomenon known as estrus. These findings are of much importance in the understanding of the etiology of some types of carcinoma. I shall now discuss the evidence for estrin, prolan, extracts of testicle, spleen and thymus, insulin and extracts of adrenal cortex.

Estrin.—Burrows and Kennaway [55] observed some interesting results from the application of estrin to the nonepilated skin of the interscapular region in male and female mice. In the males the following changes were noted: (1) scrotal hernia; (2) atrophy of the testicles; (3) diminution in the size of the seminal vesicles; (4) enlargement of the posterior lobes of the prostate, and (5) obstruction to the outflow of urine, resulting in a greatly distended bladder, due to pressure from the enlarged prostate. In the females the following conditions were noted: (1) prolonged estrus; (2) accumulation of keratinized epithelium in the vagina, which caused obstruction and distention of the passage from the uterus; (3) great enlargement of the horns of the uterus, which resulted in the formation of palpable tumors during life; (4) pyometra and perimetritis, which were the causes of death, and (5) in some cases, vaginal accumulations that prevented the flow of urine, resulting in distention of the bladder and even hydronephrosis.

53. Sugiura, K., and Benedict, S. R.: The Influence of Hormones on the Growth of Carcinoma, Sarcoma and Melanoma in Animals, Am. J. Cancer **18**:583, 1933.

54. Allen, E., and Doisy, E. A.: An Ovarian Hormone: Preliminary Report on Its Localization, Extraction and Partial Purification in Test Animals, J. A. M. A. **81**:819 (Sept. 8) 1923.

55. Burrows, H., and Kennaway, N. M.: On Some Effects Produced by Applying Oestrin to the Skin of Mice, Am. J. Cancer **20**:48, 1934.

The brilliant investigations of the English workers on the carcinogenic hydrocarbons which I have commented on in foregoing paragraphs have an added significance at this time. Since it has been shown that the aforesaid anthracene compounds are capable of producing both cancer and estrus, it is of much importance to see whether the female sex hormones can also produce, or be associated with, benign and malignant tumors. These possibilities have been realized by several workers, as will be shown in the following paragraphs. It is fairly certain that the sex hormones in the body are derived from the sterols by a process that involves a partial loss of hydrogen atoms with the formation of four condensed rings, one being aromatic in character and one containing only five carbon atoms. Thus by dehydration of the sterols the sex hormones are formed. Reviewing these researches, Sir F. G. Hopkins stated:

> It is difficult when faced with such relations not to wonder whether the metabolism of sterols, which when normal can produce a substance stimulating physiologic growth, may in very special circumstances be so perverted as to produce within living cells a substance stimulating pathologic growth.

Loeb,[56] as early as 1907, showed that it was possible to produce uterine tumors in various animals through the action of an internal secretion of the corpus luteum and mechanical factors. These formations were described as "deciduomata" and "placentomata" to indicate their tumor-like character and to emphasize the significance of such experiments for the analysis of tumor growth. Lathrop and Loeb[57] in 1916 observed that in strains of mice with a high incidence of spontaneous tumors those females that were ovariectomized before the age of 6 months showed a marked decrease in the incidence of tumors. Loeb[58] confirmed these findings in a later study. Lathrop and Loeb stated that

> these results demonstrate experimentally for the first time the significance of an internal secretion, or hormone, for the development of cancer. It is very probable that mammary cancer is not an exception, and that other substances favoring growth are a factor in the development of carcinoma in other sites. In other tissues, long continued external irritation, and in still others a combination of both factors, may, perhaps, exert a similar effect. It seems probable that any factor which periodically or over long periods of time induces increments in growth energy may be a factor in the development of carcinoma.

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56. Loeb, L.: Ueber die experimentelle Erzeugung von Knoten von Deciduagewebe, Centralbl. f. allg. Path. u. path. Anat. **18**:563, 1907.

57. Lathrop, A. E. C., and Loeb, L.: Further Investigations on the Origin of Tumors in Mice: III. On the Part Played by Internal Secretion in the Spontaneous Development of Tumors, J. Cancer Research **1**:1, 1916.

58. Loeb, L.: Further Investigations on the Origin of Tumors in Mice, J. M. Research **40**:477, 1919.

Cori [59] showed that ovariectomy in cancerous strains of mice when they are about 3 weeks of age prevents mammary cancer from developing in them. Murray [60] showed that there is a time correlation between the appearance of mammary cancer in mice and their normal sex life. He [61] was able to induce mammary cancers in castrated males with ovarian transplants, and in 1928 [62] showed, in a highly inbred strain of mice, that the presence of the ovary and of its secretions is of primary importance in the raising of the physiologic condition of the mice to the threshold of mammary carcinoma. These facts, according to Chidester,[63] show that gestation, lactation and parturition favor mammary cancer in tumorous stocks, and their absence prevents it.

Mazer [64] recently discussed the relation of some of the endocrine glands to abnormal mammary hyperplasias. The normal mammary gland depends on a pituitary-ovarian balance, and an imbalance here is believed by him to be the cause of these abnormalities of the breast. Susman [65] expressed somewhat the same view. He wrote:

> That this activity of the anterior pituitary does not in itself cause cancer is evident from the fact that in 98 per cent. of healthy pregnant females the Zondek-Ashheim reaction is positive. The relationship of malignant disease with pregnancy, in that both types of cases may give a positive Zondek-Ashheim reaction, is interesting in two ways. In both there is a tumor present, but the obvious point of difference between the two is that in pregnancy the growth is controlled —a condition lacking in the malignant growth.

Susman also stated his belief that an imbalance between the anterior and the posterior lobe of the pituitary gland is an important factor in malignant growth. Two patients with advanced cancer were treated with solution of pituitary gland alone and 5 with solution of pituitary gland and theelin. One epithelioma began to separate and was enucleated after seven weeks of treatment. The growing edge disappeared within

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59. Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas in Mice, J. Exper. Med. **45**:983, 1927.

60. Murray, W. S.: Some Effects of Ovariectomy upon Breeding Females, Science **75**:646, 1932.

61. Murray, W. S.: Factors Involved in Incidence of Spontaneous Mammary Cancer in Inbred Race of Mice, Papers Michigan Acad. Sc., Arts & Lett. **8**:411, 1928.

62. Murray, W. S.: Ovarian Secretion and Tumor Incidence, J. Cancer Research **12**:18, 1928.

63. Chidester, F. E.: Mammary Cancer and Elemental Imbalance, Am. Med. **40**:162, 1934.

64. Mazer, C.: The Endocrine Glands in Relation to Abnormal Breast Hyperplasias, with Particular Reference to Associated Nipple Bleeding and Its Treatment, M. Rec. **140**:417, 1934.

65. Susman, W.: The Rôle of the Pituitary in the Development of Cancer, Brit. M. J. **2**:794, 1931.

five days. All 7 patients showed regressive changes in the tumors, and their lives were definitely prolonged.

According to Hofbauer,[66] pregnancy in the human being is associated with hyperplastic and hypertrophic changes in the anterior lobe of the hypophysis as a response to chorionic stimuli. That radical changes occurring in association with the menopause induce certain structural alterations of the hypophysis is shown by many facts. The acquired constitutional predisposition of the multiparous woman to the development of cervical cancer during the early menopausal period is also, according to Hofbauer, due to an imbalance between pituitary and ovarian activity. He recently produced leukoplakia in the uterine cervix of the guinea-pig by repeated transplantations of bits of the anterior lobe of the pituitary gland.

Overholser and Allen [67] injected the genital hormones subcutaneously into ovariectomized monkeys. In all the animals epithelial hyperplasia occurred in the uterine cervix. In many regions, columnar epithelium was surrounded by stratified squamous epithelium. These lesions were diagnosed by Dr. James Ewing of New York City as typical of those of early cancer. Buzzi [68] stated that ovarian and uterine underdevelopment and dysfunction predispose to ovarian tumors and to uterine fibromas. Precocity and exaggerated involution, on the other hand, predispose to cancer.

Geschickter, Lewis and Hartman [69] concluded that gynecomastia (fig. 5), virginal hypertrophy (fig. 6) and fibro-adenoma are dependent on pathologic variations in the action of estrous hormone on the duct epithelium and surrounding connective tissue of the breast. This form of hypertrophy is easily produced in male animals. The condition is also prevalent in females in the prepubertal period and during the latter two thirds of pregnancy. The findings of Geschickter and co-workers permit a distinction to be drawn between hypertrophy or hyperplasia and true tumor formation. In hypertrophy, such as gynecomastia in the male and virginal hypertrophy in the female, the etiologic factor is an abnormally high concentration of estrin in the circulation acting on apparently normal breast tissue. In the formation of a tumor, on the other hand, for example a fibro-adenoma, the increased amounts of

66. Hofbauer, J.: Leucoplakia Cervicis Uteri and Early Carcinoma, Am. J. Obst. & Gynec. **27**:633, 1934.

67. Overholser, M., and Allen, E.: Ovarian Hormones and Traumatic Stimulation of Monkey's Cervix to a Condition Resembling Early Cancer, Proc. Soc. Biol. & Med. **33**:1322, 1933.

68. Buzzi, B.: Relation of Ovarian Dysfunction, Hyoplasia, and Hyper-Involution to Tumors of the Female Genitalia, Folia gynaec. **29**:339, 1932.

69. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Tumors of the Breast Related to the Oestrous Hormone, Am. J. Cancer **21**:828, 1934.

estrin in the blood act on a hypersusceptible tissue which has the capacity greatly to concentrate the hormone. This is brought about by a basic biologic variation of the developmental response in that particular tissue.

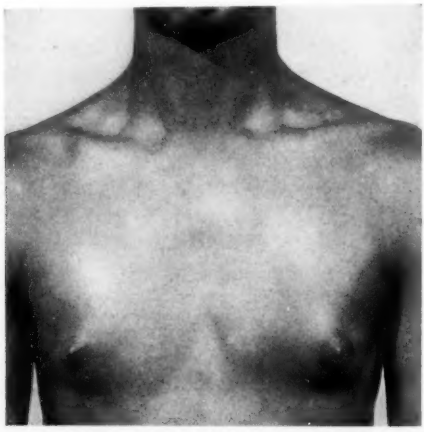

Fig. 5.—Bilateral gynecomastia in a colored boy, aged 17, more pronounced on the left side. (Courtesy of Dr. C. F. Geschickter.)

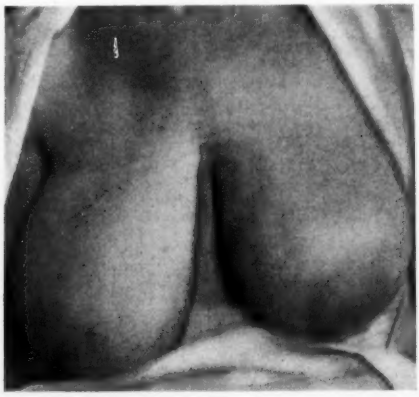

Fig. 6.—Bilateral diffuse virginal hypertrophy in a white woman of 31 years. (Courtesy of Dr. C. F. Geschickter.)

The investigators at Johns Hopkins University, as a result of their work, have shown a relationship of gynecomastia, virginal hypertrophy, fibro-adenoma, cystic disease and fibrosarcoma to the ovarian hormone estrin. This suggests new methods of diagnosis and treatment of these

conditions. This is done by an assay of the estrin in the blood. A low basal metabolic rate also reveals an increased concentration of estrin in the blood.

Recently Lewis and Geschickter [70] observed that a fibro-adenoma removed from the breast of a Negro girl yielded forty-five times as much estrin per unit of weight as normal hog ovaries (1 unit per nine grams of tumor).[71]

A softening or involution of gynecomastia was obtained by treatment with prolactin, the hormone of the anterior lobe of the pituitary gland which induces the secretion of milk; involution occurred two weeks after the injections were stopped.

The presence of estrin in cancerous areas has also been reported by Silverstein, Fellner and Engel.[72] Lacassagne [73] has reported the appearance, after repeated injections of estrin, of mammary cancer in from 50 to 80 per cent of animals belonging to two strains which normally have an incidence of cancer of only 2 per cent. Thyroxine has also been shown to inhibit tumor growth in experimental animals (Gilroy;[74] Aub and co-workers [75]).

Prolan.—The results of the aforementioned researches definitely establish that increasing concentrations of estrin are concerned in the production of a certain type of carcinoma, especially that of the mammary glands. It is also well known that the anterior lobe of the pituitary gland contains several important hormones, among which are prolan A, essential for both the normal growth and the ripening of the follicles, and prolan B, essential for luteinization and the formation of progestin (Zondek).

Leonard, Meyer and Hisaw [76] have shown that injections of estrin cause an increase in the weight of the hypophysis. This had been

70. Lewis, D., and Geschickter, C. F.: Estrin in High Concentration Yielded by a Fibro-Adenoma of the Breast, J. A. M. A. **103**:1212 (Oct. 20) 1934.

71. Lewis and Geschickter (Gonadotropic and Estrogenic Principles in a Myoma of the Uterus, J. A. M. A. **104**:45 [Jan. 5] 1935) stated that a myoma of the uterus assayed 4 units of estrin per gram of tissue, or 1,800 units per pound.

72. Silverstein, F.; Fellner, O. O., and Engel, P.: The Appearance of an Oestrous Producing Substance in the Blood Tissues Under Pathological Conditions, Ztschr. f. Krebsforsch. **35**:420, 1932.

73. Lacassagne, A.: Pathogenesis of Mammary Adenocarcinoma in the Mouse, Compt. rend. Soc. de biol. **115**:937, 1934; **114**:427, 1933.

74. Gilroy, E.: Comparison of the Effects of Arginine and Thyroxine upon Tumor Growth, Biochem. J. **24**:1181, 1930.

75. Meyer, O. O.; McTiernan, C., and Aub, J. C.: The Effect of Thyroxin upon the Metabolism of Isolated Normal and Malignant Tissue, J. Clin. Investigation **12**:723, 1933.

76. Leonard, S. L.; Meyer, R. K., and Hisaw, F. L.: The Effect of Oestrin upon the Development of the Ovary in Immature Female Rats, Endocrinology **15**:17, 1931.

observed earlier by Halpern and D'Armour,[77] who found that the hypophysis in male and female castrates given injections of estrin was 100 per cent heavier than that in controls not treated with estrin, while in normal females the weight of the pituitary gland exceeded the weight of this gland in the controls by 200 per cent. This confirms the well known fact that there is a very close physiologic relationship between the internal secretions of the anterior lobe of the pituitary gland and the ovary.

If it is true that increased concentrations of estrin predispose to malignant changes, what effect will injections of a solution of the anterior lobe of the pituitary gland have on cancerous tissue?

Zondek[78] was the first to show that the urine of patients with malignant tumors contains a hormone similar to that of the anterior lobe of the pituitary gland, especially that of patients with genital carcinoma. This finding has been confirmed by Dodds[9] and others. Ferguson[79] studied the excretion of prolan A in the urine in 117 consecutive cases of teratoma testis. This amounted to from 50 to 50,000 mouse units per liter of urine. Local recurrence or metastasis was accompanied by an increase of prolan A in the urine. Observations at autopsy revealed the important relation between the hormone of the anterior lobe of the pituitary gland and epithelial hyperplasia in the genital organs of the male, especially in the prostate and seminal vesicles.

Zondek and co-workers[80] recently studied the effect of prolan on the growth of the Ehrlich mouse carcinoma. Eighteen hundred mice were used, and the tumors "took" in 100 per cent of the cases. The mice were killed twenty-three days after the injection of prolan, and the tumors were cut and weighed. The average weight of 247 control tumors was 1.65 Gm. The average weight of the tumors of 250 animals which had been treated with thyroxine, epinephrine or folliculin was 1.55 Gm. The average weight of the tumors in 405 mice treated with prolan was only 0.2 Gm.

The effect of prolan has also been observed by other workers. For instance, Moller[81] used 70 male mice weighing from 10 to 12 Gm. and bearing the Ehrlich mouse carcinoma (which does not regress

77. Halpern, S. R., and D'Armour, F. E.: Effects of Oestrin upon Gonads, Mammary Glands and Hypophysis of the Rat, Proc. Soc. Biol. & Med. **32**:108, 1924.

78. Zondek, B.: Ueber die Hormone des Hypophysenvorderlappens: III. Follikelreifungshormon (Prolan A) und Tumoren, Klin. Wchnschr. **9**:679, 1930.

79. Ferguson, R. S.: Quantitative Behavior of Prolan A in Teratoma Testes, Am. J. Cancer **18**:269, 1933.

80. Zondek, H.; Zondek, B., and Werner, H.: Prolan and Tumor Growth, Klin. Wchnschr. **18**:137, 1933.

81. Moller, H.: Relation Between Tumor Growth and the Hormone of the Anterior Hypophyseal Lobe, Am. J. Cancer **20**:67, 1934.

spontaneously in the strain used). Just before inoculation the animals were divided into two groups: Thirty received no treatment. Forty were given 50 rat units of prolan daily from the first to the tenth day, the dose being then increased to 200 rat units, which was given from the sixteenth to the twenty-second day. The animals were killed on the twenty-third day, and their tumors were removed and weighed. The average weight was 0.22 Gm. as compared with 1 Gm. for the untreated controls. This confirms the work of Zondek with comparable doses. It was also observed (in confirmation of the work of Zondek) that the tumors from the prolan-treated mice were so reduced in vigor of growth as to be no longer transplantable. At autopsy all prolan-treated mice showed the well known enlargement of the generative organs, that is, striking hypertrophy and hyperplasia of both adrenal glands, with the microscopic changes corresponding to pregnancy. This hypertrophy of the adrenal glands Moller believed to be most important. It is possible that prolan stimulates the adrenal cortex to secrete more of a new hormone, which then causes regression of the tumor.

Cannavo [82] injected prolan into 30 experimental mice in each of two series inoculated with a mouse carcinoma. Thirty mice without injections of prolan were used as controls. Fifteen hundred rat units of prolan caused a retardation in the growth of the tumor in only 2 of 30 animals, but 2,300 units (800 before and 1,500 after inoculation) caused definite and constant retardation. The results of these investigations with prolan have been confirmed by Ludwig and von Ries.[83]

The evidence presented shows that increased concentrations of estrin favor the production of malignant changes while injections of prolan (possibly by stimulating the adrenal glands with resultant hypertrophy) tend to cause regression of cancerous growth. It is also possible that the loss of prolan in the urine of patients with cancer, as observed by Zondek and others, favors increased production of estrin, with resultant malignant changes. On the other hand, the marked hypertrophy of the pituitary gland following injections of estrin, as observed by Halpern and D'Armour,[77] may be responsible for the increased excretion of prolan in the urine of patients with cancer. Prolan is then lost to the body, and this possibly creates an imbalance between prolan and estrin favoring the development of malignant growths. While this is mere speculation, it is nevertheless of importance in the future to study this antagonistic relation between prolan and estrin in the development of some types of cancer.

82. Cannavo, L.: Influence of Prolan on the Growth of Inoculated Mouse Carcinoma, Riforma med. **49**:278, 1933.

83. Ludwig, F., and von Ries, J.: Hormone, Vitamine, Zwellwachstum und Karzinom, Schweiz. med. Wchnschr. **64**:141, 1934.

Extracts of Testicle, Spleen, Thymus and Parathyroid Gland and Placenta.—Hoffman, Parker and Walker [84] stated that extract of rabbit testicle markedly enhanced the growth of chicken tumor I. These results were obtained when tumor mash or cell-free filtrates were used in the inoculations. Duran-Reynals and Claude [85] confirmed these results. They showed that the agent of chicken tumor I was spread when it was injected together with an extract of testicle, and that the resultant lesions were greatly enhanced. On the other hand, Duran-Reynals [86] showed that an extract of rat, rabbit or bull testicle prevents or retards the growth of a rabbit tumor when a mixture of the extract and a suspension of the tumor cells is inoculated intradermally. Similar mixtures made with normal rabbit serum instead of extract of testicle greatly enhanced the growth of the tumors.

Matsuoka [87] observed that splenectomy favored the growth of the Kato rabbit sarcoma. In the absence of the spleen the glycolytic activity of the neoplasm was augmented. Treatment with various preparations of spleen inhibited more or less the growth of this sarcoma. Fischera [88] recently observed that certain organs (spleen, bone marrow, thymus) or their extracts are inimical to tumor growth, whereas others (testes, ovary) are especially favorable. Murphy and Sturm [89] showed that

Extracts of desiccated homologous embryo skin and placenta decrease markedly the rate of postoperative local recurrence after the surgical removal of spontaneous cancer of mice. Autografts after a short period of contact with these extracts either failed to grow, or, in the majority of instances, their subsequent growth was definitely retarded. Intraperitoneal injection of the extracts was followed by cessation of growth of established tumors in more than two-thirds of the animals treated, and among these many of the tumors regressed and over 20 per cent were completely absorbed. Tumor mice treated with either extract rarely developed new malignant foci, though this happened frequently in untreated mice.

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84. Hoffman, D. C.; Parker, F., and Walker, T. T.: Effect of Testicle Extract on Rous Sarcoma, Am. J. Path. **7**:523, 1931.

85. Duran-Reynals, F., and Claude, A.: Further Experiments on the Effect of Testicle Extract on the Agent of Chicken Tumor I, Proc. Soc. Exper. Biol. & Med. **32**:67, 1934.

86. Duran-Reynals, F.: The Effect of Testicle Extract and of Normal Serum on the Transplantable Epithelial Tumor of the Rabbit, J. Exper. Med. **54**:493, 1931.

87. Matsuoka, H.: Effect of Spleen on the Growth of Transplanted Tumor, Jap. J. Obst. & Gynec. **17**:25, 1934.

88. Fischera, G.: Significance for Tumor Genesis of Disturbances in Organ Equilibrium and Organotherapy for Malignant Neoplasms, Klin. Wchnschr. **12**: 1957, 1933.

89. Murphy, J. B., and Sturm, E.: The Effect of a Growth Retarding Factor from Normal Tissues on Spontaneous Cancer in Mice, J. Exper. Med. **60**:305, 1934.

Maigin [90] also observed a good prophylactic effect following the use of placenta in the form of a fresh graft or of an injected extract with surgical, roentgen and radium treatment. Of 30 patients treated, 10 were still living after five years, while the other 20 were patients recently treated. While it is difficult to judge whether the beneficial effects here were due to surgical, roentgen, radium or placental treatment, nevertheless, at the present time, the use of endocrine products in addition to these other means of treatment in some types of carcinoma is more than justified. Maisin [91] observed that organotherapy (brain, thymus and spleen) had an active inhibitory effect on the course of tar cancers. Maisin, Pourbaix and Picard [92] observed that ethereal extracts of spleen, brain, thymus and liver, when injected subcutaneously, had an inhibitory effect on the neoplasms of animals and man. The animal tumors were spontaneous mammary carcinomas of the mouse, tar cancers of the mouse and rabbit and a carcinoma of the mamma of the dog. In the human patients the metastasizing carcinomas or sarcomas were beyond the hope of cure by surgical or radium treatment.

Gwyer [93] was probably the first to use dried thymus gland in the clinical treatment of cancer. This therapy was found to diminish or eliminate pain, lessen the size of the growth and improve greatly the metabolic condition of the patient. In his second study [94] the thymus treatment was given to 16 patients with inoperable, incurable and hopeless cancers of various types.

Gwyer summarized his findings as follows:

> The foregoing histories of cancer cases present several prominent points, *viz.*
>
> 1. With the exception of two or three cases all showed temporary improvement in that there was (a) less pain, (b) reduction in growth, (c) general condition better. This improvement was quite prompt in making its appearance.
>
> 2. Several of the patients died or at present are near their end.
>
> 3. Many of those that died did not succumb as the cancer patient ordinarily does, in that (a) there was no great loss in weight, (b) no leaden pallor and other visible signs of cachexia, and (c) no local increase of the cancer. On the other hand, at least two of the fatal cases continued fairly well nourished, with

90. Maigin, A. C.: New Treatment of Cancer, Bull. Soc. d'obst. et de gynéc. **20**:316, 1932.

91. Maisin, J.: Organotherapy by Mouth in Experimental Cancer, Compt. rend. Soc. de biol. **107**:916, 1931.

92. Maisin, J.; Pourbaix, Y., and Picard, E.: Experiments on Organotherapy of Cancer by Subcutaneous Injection, Compt. rend. Soc. de biol. **107**:918, 1931.

93. Gwyer, F.: Thymus Gland Treatment of Cancer: A Preliminary Report with Presentation of a Case of Inoperable Cancer with Great Relief of Symptoms, Ann. Surg. **46**:89, 1907.

94. Gwyer, F.: On the Thymus Gland Treatment of Cancer, Ann. Surg. **47**: 506, 1908.

clear skin, red mucous membranes, and an actual and marked reduction of the cancer growth, with no evidence of metastases. The same is true of some still living.

Hanson [95] treated 4 patients who had inoperable carcinomas with daily injections of thymus extract. Definite improvement was observed, with necrosis and absorption of part of the tumors.

Recently Rowntree, Clark and Hanson [96] reported some remarkable results obtained on the growth of succeeding generations of rats by treating the parent rats with Hanson's thymus extract. Table 2, taken from their paper, gives these results.

The number and size of the litters and the weight at birth increased very greatly in these cases. The third generation of rats whose parents were treated with thymus extract were much larger at birth and showed striking precocity in growth and development, early eruption of teeth,

TABLE 2.—*Development of Thymus-Treated Rats Contrasted with That of Controls (from Rowntree, Clark and Hanson [96])* *

	Controls	F_1	F_2	F_3	F_4
Average weight at birth, Gm.†	4.6	5.1	5.3	5.3	5.3
Ears opened, days	2½-3½	2	1-2	1	1
Teeth erupted, days	8-10	1-9	1-2	1	1
Hair appeared, days	12-16	3-12	4-6	4-5	2-3
Eyes opened, days	14-17	12-14	4-6	4-6	2-3
Testes descended, days	35-40	†15-29	†5-21	†5-12	4-5
Vagina opened, days	55-62	†30-45	†23-32	†21-27	18-19

* The figures in this table are based on a somewhat different setup compared with those published in Science and in the detailed paper, which will appear later.
† The low numbers usually refer to late litters in the generation and the high numbers to the first litters born.

appearance of the fur, opening of the eyes, descent of the testes and opening of the vagina. It is therefore evident that thymus extract is by far the most active growth-promoting hormone known. This discovery opens a new field for the investigation of problems related to growth.

Inuzuka [97] showed that parathyroid hormone when injected into rabbits bearing sarcoma and carcinoma inhibited the growth of these tumors. A partial extirpation of the parathyroid glands increased the rate of growth of the tumors. The effect of total parathyroidectomy could not be determined accurately, owing to the development of tetany.

95. Hanson, A. M.: The Bovine Thymus, Minnesota Med. **13**:17, 1930; Treatment of Cancer with Thymus Extract, Correspondence, J. A. M. A. **94**:653 (March 1) 1930.

96. Rowntree, L. G.; Clark, J. H., and Hanson, A. M.: The Biological Effects of Thymus Extract (Hanson), J. A. M. A. **103**:1425 (Nov. 10) 1934.

97. Inuzuka, A.: On the Influence of the Parathyroid Glands upon the Development of Malignant Tumors, Tr. Jap. Path. Soc. **23**:680, 1933.

Paik,[98] on the other hand, found that the internal secretion of the parathyroid glands stimulated the growth of rat carcinoma, while decrease of this secretion interfered with the development of carcinoma. These results are difficult to reconcile with those of Inuzuka, but it is possible that the parathyroid hormone affects the growth of the tumor either favorably or unfavorably.

Insulin.—After Warburg [2] and others had shown that there is a defect in the metabolism of carbohydrate in cancer, it was reasonable to expect that insulin might have a beneficial effect on certain types of malignant tissue. This possibility has been realized.

Da Costa [99] observed that the local application of insulin caused a regression in the growth of skin cancer. Lambret and Driessens [100] observed the complete disappearance of Jensen rat sarcoma in 30 of 40 cases under the influence of insulin injected after the tumors were grafted. Kawamura and Kamikawa [101] inhibited the production of tar tumors by injections of insulin, but injections of epinephrine enhanced their production. Konsulov and Dimitrakov [102] inhibited the growth of spontaneous tumors and of Ehrlich's mouse tumor in those in whom it was grafted, with injections of insulin. Further work with insulin in this connection will be awaited with much interest.

Extracts of Adrenal Cortex.—Although several investigators have obtained negative results with extracts of adrenal glands in the treatment of experimental tumors of animals, other workers have obtained positive results. While it is difficult in this connection to judge negative results, it should not be forgotten that the variability in different types of tumors, in animals and in human beings and, most important of all, the variability in the potency of extracts are factors that should be evaluated before negative results are accepted. The activity of hormones can easily be destroyed if the details of the technics for their preparation are not followed closely. Again, an extract that is effective in one patient may not be effective in another with an identical type of

98. Paik, T. S.: On the Relationship Between the Parathyroid Hormone and the Growth of Rat Carcinoma, Am. J. Cancer **15**:2756, 1931.

99. da Costa, F. G.: Effect of Insulin on Carbohydrate Metabolism in Cancer of Skin, Compt. rend. Soc. de biol. **107**:85, 1931.

100. Lambret, O., and Driessens, J.: Regression and Disappearance of Jensen Sarcoma under the Influence of Insulin Injected after Grafting, Compt. rend. Soc. de biol. **112**:1430, 1930; **116**:1068, 1934.

101. Kawamura, M., and Kamikawa, Y.: Relation Between the Production of Tar Tumors and the Organs of Internal Secretion Which Have a Special Relation to the Metabolism of Carbohydrate, Am. J. Cancer **15**:2835, 1933.

102. Konsulov, S., and Dimitrakov, K.: The Cancer Problem as a Hormone Problem, Am. Univ. Sofia Facult. phys.-math., 1933, vol. 28, no. 3; Ztschr. f. Krebsforsch. **36**:37, 1932.

carcinoma. An extract of a certain gland should not be expected to be effective in a certain type of tumor if there is no physiologic connection between the gland and the structure in which the tumor is growing.

For example, extracts of adrenal cortex should be expected to exert their best effect on carcinomas and sarcomas of the reproductive system (the breast excepted) and the urogenital system, rather than on those of the tongue and face. Again, the lactation-promoting hormone of the anterior lobe of the pituitary gland, prolactin, would be expected to affect the growth of mammary tumors. Also a transplantable tumor in an animal with a normal endocrine system may or may not be the same as, for instance, a carcinoma of the cervix in a woman whose endocrine system may or may not be normal. These and many other factors add to the uncertainty of negative results. Until the hormones are isolated in a chemically pure state and their effects on the growth of tumors are observed by a number of different workers, we may expect differences of opinion as to their value or nonvalue in different experimental and clinical conditions.

This confused state of affairs, however, is no justification for abandoning endocrine therapy in malignant conditions. The best procedure at present is simply to record the results obtained and evaluate these some time in the future when more data are available.

Boris Sokoloff [103] was the first to publish data on the beneficial effects of extracts of the cortex of the adrenal gland (fortified with iron and tri-naphthyl-para-rosanalin sulphate) on tumors. Working at the Rockefeller Institute for Medical Research in 1928, he noticed that in cancerous chickens the cortex of the adrenal gland grew to five times its normal size. The cortex was also very sensitive to the malignant neoformations. Later, at the meeting of the International Physiological Congress in Boston in 1929, he gave a demonstration of the liquefaction of malignant tumors with this extract. The mice and rats were the bearers of four kinds of tumors: rat sarcoma no. 10, rat sarcoma no. 39, mouse sarcoma no. 180 and F. R. sarcoma. All these animals were from the stock of the Institute for Cancer Research of Columbia University. About 1,000 experiments were performed. It was observed that the process of liquefaction began very rapidly: In small tumors scleroses set in within from three to five days. Larger tumors dissolved in about two weeks. Rapid liquefaction caused the death of some of the animals.

103. Sokoloff, B.: Physiological Studies of Malignant Cells: Preliminary Communication, abstr., Proc. Internat. Physiol. Congress, 1929, p. 251; Studies on the Adrenal Cortex: I. Changes in the Adrenal Cortex and Its Reticulo-Endothelial Cells Under the Influence of Transplanted Tumors, Arch. f. exper. Zellforsch. **11**:112, 1931; II. Liquefaction of Malignant Tumors, ibid., p. 114.

This important work of Sokoloff, which attracted little attention at the Congress, has since been confirmed by several other workers. Auler and Rubenow [104] prepared an extract from the adrenal cortex which when injected into rats bearing the Jensen sarcoma or the Flexner-Jobling carcinoma caused regression in the tumors in a certain number of animals. Arloing, Morel, Josserand and Badinand [105] found that injections of a protein precipitate from glycerin extracts of calves' adrenal glands greatly inhibited the growth of an experimental mouse tumor. Vassiliadis [106] prepared an ether-acetone extract of adrenal glands and hypophysis, to which an alcoholic solution of magnesium chloride was added. The precipitate was collected and suspended in water, and a dose equivalent to 0.5 Gm. of fresh tissue was injected into mice which were receiving applications of tar. Only 40 per cent of the mice thus treated had developed tumors at the end of two hundred and forty days, while 100 per cent of the controls, treated only with tar, had developed tumors. The antiblastic substance was also stated to occur in brain, bone marrow, thymus and other tissues. Sano [107] observed that treatment with testicle and adrenal gland had an inhibitory influence on the growth of the Fujinami chicken myxosarcoma in vitro. Vles, de Coulon and Ugo [108] observed that the feeding of adrenal gland, testicle and digestive tube produced a considerable decrease in the incidence of cancer produced by tar in experimental animals.

Arloing, Josserand and Charachon [109] observed an inhibition of the growth of a mouse carcinoma after the subcutaneous transplantation of the adrenal gland from a rabbit prepared by inoculations of the same tumor. A glycerin extract was equally effective. Arloing [110] observed

104. Auler, H., and Rubenow, W.: Relation Between the Adrenals and Neoplastic Growth, Ztschr. f. Krebsforsch. **33**:292, 1930.

105. Arloing, F.; Morel, A.: Josserand, A., and Badinand, A.: Further Studies on the Tumor Inhibiting Properties of Adrenal Extracts Tested on Experimental Epithelioma in White Mice, Compt. rend. Soc. de biol. **112**:156, 1933.

106. Vassiliadis, H.: Existence of Antiblastic Substances in the Adrenals and Hypophysis, Compt. rend. Soc. de biol. **115**:1241, 1934.

107. Sano, A.: The Influence of Hormones on the Growth of Transplantable Chicken Myxo-Sarcoma Cultivated in Vitro, Tr. Jap. Path. Soc. **21**:805, 1931.

108. Vles, F.; de Coulon, A., and Ugo, A.: Investigations on the Physicochemical Properties of Tissues in Relation to the Normal or Pathological State of the Organism: XVII. Recent Studies on the Statistical Evolution of Cancer as Caused by Tarring. Arch. de phys. biol. **10**:304, 1933.

109. Arloing, F.; Josserand, A., and Charachon, J.: Modifications évolutives de l'épithélioma expérimental de la souris blanche par greffes de surrénales provenant de lapins préparés avec ce même épithélioma, Compt. rend. Soc. de biol. **100**:1035, 1929.

110. Arloing, F.: Further Investigation of Retarding Action of Suprarenal Extracts on Transplantable Mouse Carcinoma, Am. J. Cancer **19**:406, 1933.

that an extract of calves' adrenal glands contained an agent capable of retarding the growth of a transplantable mouse carcinoma. The average weight of the tumors in the treated animals was 0.73 Gm., whereas in the untreated controls it was 4.04. Gm.

The foregoing evidence justifies the view that, contrary to the opinion of many workers, the adrenal gland contains an anticarcinogenic substance. From my chemical work on an active extract of adrenal gland I am convinced that the anticarcinogenic substance here is different from the cortical hormone of Swingle and Pfiffner and others. This view is based on the difference in the chemical properties of the two hormones. This fact shows that it would be unprofitable to use the cortical hormone in the clinical treatment of malignant conditions.

SULPHYDRYL COMPOUNDS

At the present time biochemists are showing much interest in the metabolism of oxidized and reduced sulphur compounds as cystine, cysteine, methionine, glutathione, insulin and the posterior pituitary hormones. It has long been known that proteins containing organic sulphur, as in cystine and methionine, are the chief sources of sulphur in metabolism, and that organic sulphur is necessary for growth. In this country the chief workers in this important field at the present time are Lewis, Sherwin, Brand, Voegtlin, Sullivan, du Vigneaud, Hammett and their coworkers, most of whom read interesting papers in a symposium on sulphur metabolism before Section N of the American Association for the Advancement of Science at the recent meeting in Pittsburgh. Hammett [111] and Reimann and Hammett [112] discussed the importance of sulphydryl (—SH) [113] from both the physiologic and the pathologic point of view, and are now using sulphydryl compounds to bring about healing of long-standing ulcers and bedsores which have hitherto resisted all therapeutic effort.

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111. Hammett, F. S.: Natural Chemical Factors in Growth and Development: Symposia on Quantitative Biology, Long Island, N. Y., Cold Spring Harbor Biological Laboratory, 1934, vol. 2, p. 78.

112. Reimann, S. P., and Hammett, F. S.: Cell Proliferation Response to Sulphydryl in Man, Proc. Soc. Exper. Biol. & Med. **27**:20, 1929.

113. Sulphydryl (—SH) is the name given to the reduced sulphur group of cysteine, two molecules of which are supposed to be formed in the metabolism of a molecule of the amino-acid cystine in the body, as follows:

Some seven years ago Hammett [114] and co-workers began their extensive studies on factors that control normal and pathologic growth. They desired to know whether lead, which Blair Bell had already reported to be a retardant of embryonic growth, was an inhibitor of growth with regard to cell number or with regard to cell size or assimilation. The results of their work showed that lead inhibits cell growth in number rather than in size. This fact gave rise to the view that lead removes some chemical entity essential to multiplication. Further work showed that the precipitate consisted of lead with an unoxidized sulphur grouping similar to that in glutathione, which presumably was sulphydryl. This reduced sulphur compound is present in largest amounts where mitosis is most active. Thus it seems probable that lead, by precipitation of the sulphydryl, may inhibit cell division. Toennies recently prepared some suboxidized derivatives of cysteine which, according to Hammett and Hammett,[115] comprise a naturally occurring chemical equilibrium which is specifically essential to the regulation of the proliferative phase of developmental growth.

According to Hammett,[116] the relationship of these findings to the problem of cancer depends entirely on the significance of proliferation to malignant growth, with especial emphasis on those factors which are conducive to malignant growth. It was shown that the potential proliferation of immature cells is greater than that of more mature cells, and that immature cells are more sensitive to the action of sulphydryl, which is found in high concentration where cell division is most active. Hammett expressed the belief that control of the proliferative phase of cancer can be obtained (1) by discovering ways of decreasing the sulphydryl content of tumor tissue or (2) by introducing the partially oxidized derivatives (sulphoxides) of the accelerating (—SH) groups. He summarized the matter as follows:

> From what has gone before it would seem that a partial solution of the cancer problem rests upon the discovering of naturally occurring chemical factors determinative of cell maturity. Towards this an attempt has been under way for the past three years to ascertain whether or not any of the amino acids and nucleic acid derivatives have any specific influence upon any particular developmental activity. Results have been obtained which are in press. The work is still in progress and probably will be for many years to come.

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114. Hammett, F. S.: The Influence of Sulphydryl on Cell Proliferation and Its Possible Significance in the Cancer Problem. Paper read in the Symposium on Sulfur Metabolism, Sect. N, American Association for the Advancement of Science, in Pittsburgh, Dec. 29, 1934.

115. Hammett, D. W., and Hammett, F. S.: Crucial Demonstration of the Proliferative Growth Regulating Property of the Naturally Occurring Chemical Equilibrium Composed of Sulphydryl and Its Partially Oxidized Derivatives, Protoplasma **19**:161, 1933.

116. Hammett, F. S.: Cancer as a Problem in the Biology of Cell Division, Tr. Coll. Physicians, Philadelphia **54**:136, 1932. Hammett.[114]

SUMMARY

Cancer as a problem in metabolism has been reviewed under the following headings: carbohydrate metabolism of tumors; lipoid metabolism and cholesterol; irradiation and carcinoma of the skin; the carcinogenic hydrocarbons.

Endocrine imbalance in the pathogenesis of some types of cancer was reviewed under headings as follows: estrin; prolan; extracts of testicle, spleen, thymus and parathyroid gland; insulin; extracts of adrenal cortex.

While it is difficult at present to distinguish cause and effect in the newer experimental work on cancer reviewed in this paper, the following concepts are worthy of serious consideration by students of the problem.

1. In malignant tumors the metabolism of carbohydrate is abnormal, resulting in low respiration and high glycolysis.

2. Lipoids and cholesterol are definitely increased, the latter especially in carcinoma of the skin.

3. Massive doses of ultraviolet radiation may produce cancerous lesions about the eyes, ears and head of the experimental animal.

4. Hydrocarbons containing the phenanthrene group and estrin are both carcinogenic and estrogenic.

5. The chemical relationship of the bile acids, sterols, sex hormones and carcinogenic hydrocarbons is established.

6. Injections of prolan may inhibit the growth of some types of tumors.

7. Extracts of adrenal cortex, thymus and spleen and insulin may also have a retarding influence on some types of experimental tumors.

8. The relation of sulphydryl (—SH) to the problem of cancer was discussed.

Dr. F. S. Hammett of the Lankenau Hospital Research Institute of Philadelphia allowed me to summarize, in advance of publication, his recent paper, "The Influence of Sulphydryl on Cell Proliferation and Its Possible Significance in the Cancer Problem," read before Section N of the American Association for the Advancement of Science recently in Pittsburgh.

BACTERIOLOGY OF NORMAL AND DISEASED GALLBLADDERS

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Previous studies of the flora of diseased gallbladders have revealed the presence of a wide variety of micro-organisms. One school has placed the blame for cholecystitis on organisms of the colon bacillus group, which grow so rapidly in bile. Most writers of the older literature take this attitude. On the other hand modern observers and especially experimenters are inclined to implicate the streptococcus, which is also a common inhabitant of the gallbladder. Rosenow,[1] Wilkie [2] and Magner and Hutcheson [3] have reviewed the recent literature on this subject and made significant contributions. It seems undoubtedly true that experimental cholecystitis is best produced by the streptococcus.

However, since the time of Osler [4] a significant point has received but little attention, namely, the fact that even in the presence of severe pathologic damage to the gallbladder the bile or fluid contents are sterile in a large majority of cases. Osler reported sterile findings in 52 per cent of the cases. More recent studies have materially increased this figure. Magner and Hutcheson's review of the American literature shows a tabulation of the results in 1,340 cases from thirteen different clinics; in 65 per cent of the cases sterile contents were found. This (65 per cent) is the exact incidence found in our own studies. Usually the wall of the gallbladder has yielded bacteria about twice as frequently as the contents, which fact may be explained on the basis of lymphoid tissue in and around the wall of the gallbladder especially near the

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1. Rosenow, E. C.: The Etiology of Cholecystitis and Gallstones and Their Experimental Production by the Intravenous Injection of Bacteria, J. Infect. Dis. **19**:527, 1916.

2. Wilkie, A. L.: The Bacteriology of Cholecystitis, Brit. J. Surg. **15**:450, 1928.

3. Magner, W., and Hutcheson, J. M.: Cholecystitis, Canad. M. A. J. **17**:469, 1932.

4. Osler, W.: Modern Medicine, Philadelphia, Lea Brothers, 1907.

ducts. The fact has been overlooked by many that the lymphoid tissue is one of the chief filter basins in the body for foreign material; hence it tends to concentrate the bacteria more in the wall than in the bile.

In view of these facts it was felt that in order to elucidate the relationship of bacteria to disease of the gallbladder, more detailed studies were necessary. One must know not only the type of bacteria but their number. The intimate relation of the gallbladder to the intestine with its rich flora and the close lymphatic connection between the two have been emphasized by Graham and Peterman.[5] Furthermore, the fact that flora of the normal liver is surprisingly rich (as revealed by the work of Ellis and Dragstedt,[6] Andrews and Hrdina,[7] Andrews, Rewbridge and Hrdina,[8] Berg, Faw and Jobling,[9] Dvorak[10] and others) also emphasizes the fact that the gallbladder lies in a far from sterile locale and that in order to attribute pathogenicity to any bacteria found it must be shown that they exist in numbers compatible with the recognized conception of a true infection. All the authorities emphasize the fact that the gallbladder is a favorite lurking place for bacteria (Osler,[4] Kaufmann,[11] Rolleston and McNee[12] and Graham and his co-workers[13]). These organisms do not necessarily cause infection. This point will be discussed in greater detail later but is mentioned to show the necessity of knowing something quantitative about the flora of the gallbladder in different stages of activity or quiescence.

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6. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, Arch. Surg. **20**:8 (Jan.) 1930.

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12. Rolleston, H. D., and McNee, J. W.: Diseases of Liver, Gall-Bladder and Bile Duct, New York, The Macmillan Company, 1929.

13. Graham, Evarts Ambrose; Cole, Warren H.; Copher, Glover H., and Moore, Sherwood: Diseases of the Gall-Bladder and Bile Duct, Philadelphia, Lea & Febiger, 1928.

METHODS

The material reported on consists of cultures made on ninety-one gallbladders and their contents removed surgically at the clinics of the University of Chicago.

Immediately after removal from the abdominal cavity the intact gallbladder was placed in a sterile specimen container, covered and taken to the laboratory. Within a short time the bile was aspirated through the wall with a sterile needle and syringe and placed in a sterile test tube. Then, with sterile scissors and forceps, 1 or 2 Gm. of tissue was removed, usually from the fundus of the gallbladder, placed in sterile mortar with sand and saline solution and ground vigorously. This macerated piece of tissue with the saline solution was then cultured in a deep brain tube, the tissue being placed well below the surface of the brain, thus giving an ideal condition for growth of both aerobic and anaerobic organisms. The bile was cultured not only in the deep brain tube but also on a blood agar plate, and 0.1 cc. of bile was placed in a poured agar plate. The latter procedure was carried out for the purpose of estimating the number of organisms per cubic centimeter of bile. Thus a quantitative estimation of the infection in the bile was obtained. The plates were incubated for seventy-two hours before being labeled "no growth." The brain tubes were examined each day for the first five days, smears being made which were stained by Gram's method and searched for organisms; at the same time transfers were made from the brain tubes to the surface of blood agar plates. After the fifth day the tubes were examined every two or three days, and no tube was discarded as sterile before twenty-one days had elapsed.

All organisms isolated were identified by standard bacteriologic procedures. Thus in the bile definite counts could be made in most cases. However, in cases in which anaerobes were found a quantitative estimation was not made, as anaerobic plates were not made on the original bile.

The ninety-one gallbladders were classified into five groups (tables 1 to 5): Group 1 comprised normal gallbladders. This classification was based on the histologic and gross picture. Some patients whose gallbladders were included in this series had had fairly typical biliary colic, and one had had jaundice, but in all the disease had been quiescent for long periods when the operation was performed. Group 2 comprised normal gallbladders with stones; group 3, gallbladders from patients with obstruction of the common duct, and groups 4 and 5, gallbladders from patients operated on in the active and quiescent stages of the disease, respectively. The gallbladders in groups 4 and 5 were classified wholly on the basis of the clinical symptoms; all showed varying degrees of pathologic change, and nearly all contained stones. Those from patients operated on in the active stage included all those obtained at operation performed within five days of a typical biliary colic. Those from patients operated on in the quiescent stage were from patients who had been free from symptoms for more than five days before operation; many were from patients who had been symptomless for long periods. Some patients had never had attacks of colic, the diagnosis having been made by roentgen examination.

ANALYSIS OF RESULTS

A general survey of results is given in table 6. It can be seen at once that our figures correspond in a rough way with those of previous investigators. In about two thirds (67 per cent) of the cases the bile

TABLE 1.—*Results of Cultures of Normal Gallbladders*

Number	Wall	Bile	Colonies per Cc.
1	Sterile	Sterile	
2	Sterile	Sterile	
3	Staphylococcus albus	Sterile	
4	Gram-negative spore former	Gram-negative spore former	5
5	Sterile	Sterile	
6	Bacillus Welchii	Sterile	
7	Sterile	Sterile	
8	Sterile	Sterile	

TABLE 2.—*Results of Cultures on Normal Gallbladders Containing Stones*

Number	Wall	Bile	Colonies per Cc.
1	Bacillus Welchii	Sterile	
2	Bacillus coli, staphylococci	Bacillus coli, staphylococci	350
3	Gram-positive diphtheroids	Gram-positive diphtheroids	2,610
4	Sterile	Sterile	
5	Streptococcus viridans	Streptococcus viridans	50,000
6	Sterile	Sterile	
7	Bacillus Welchii	Bacillus Welchii	
8	Sterile	Sterile	
9	Sterile	Sterile	
10	Few diphtheroids and streptococci	Sterile	
11	Sterile	Sterile	
12	Staphylococci albus (few)	Sterile	

TABLE 3.—*Results of Cultures of Gallbladders from Patients with Obstruction of the Common Duct*

Number	Diagnosis	Wall	Bile	Colonies per Cc.
1	Stone	Bacillus coli, Bacillus Welchii	Bacillus coli, Bacillus Welchii	Innumerable
2	Portal suppuration	.....	Bacillus coli	Innumerable
3	Stone, quiescent	Bacillus coli, Bacillus Welchii	Bacillus coli, Bacillus Welchii	Innumerable
4	Carcinoma of pancreas	No culture made	Bacillus coli, Bacillus Welchii	Innumerable

proved to be sterile, while 51 per cent of the cultures from the walls were found to be sterile (table 8). It has been assumed by several previous investigators [3] that the finding of staphylococci represented contaminations due to the handling of the tissues in grinding. If this view were adopted it would considerably increase the percentage of

TABLE 4.—*Results of Culture of Gallbladder from Patients Operated on During Quiescent Stage of Disease*

Number	Wall	Bile	Colonies per Cc.
1	Sterile	Sterile	
2	Few staphylococci	Sterile	
3	Sterile	Sterile	
4	Sterile	Sterile	
5	Sterile	Sterile	
6	Bacillus coli	Bacillus coli	Innumerable
7	Sterile	Sterile	
8	Bacillus typhosus	Sterile	
9	Sterile	Sterile	
10	Staphylococcus aureus	Sterile	
11	Sterile	Sterile	
12	Sterile	Sterile	
13	Sterile	Sterile	
14	Sterile	Sterile	
15	Sterile	Sterile	
16	Bacillus coli	Bacillus coli	
17	Sterile	Sterile	
18	Sterile	Sterile	
19	Streptococcus viridans, staphylococci	Bacillus Welchii	
20	Sterile	Sterile	
21	Sterile	Sterile	
22	Staphylococci, Bacillus Welchii	Streptococci	50
23	Sterile	Staphylococci	Few
24	Sterile	Micrococcus flavus	
25	Bacillus coli	Bacillus coli	Innumerable
26	Sterile	Sterile	
27	Diphtheroids	Diphtheroids	88
28	Few anaerobic streptococci	Sterile	
29	Few streptococci, staphylococci	Sterile	
30	Few streptococci, staphylococci	Streptococci, staphylococci	Few
31	Sterile	Sterile	
32	Sterile	Sterile	
33	Bacillus subtilis (few)	Sterile	
34	Staphylococci	Sterile	
35	Gram-negative rods	Gram-negative rods	Innumerable
36	Sterile	Sterile	

TABLE 5.—*Results of Cultures of Gallbladders from Patients Operated on During Active Stage of Disease*

Number	Wall	Bile	Colonies per Cc.
1	Staphylococci; Bacillus coli	Staphylococci; diphtheroids; Bacillus coli	Innumerable
2	Staphylococcus albus	Staphylococcus albus	
3	Sterile	Sterile	
4	Sterile	Sterile	
5	Sterile	Sterile	
6	Gram-negative spore former	Gram-negative spore former	25
7	Sterile	Staphylococci	100
8	Sterile	Sterile	
9	Sterile	Sterile	
10	Sterile	Sterile	
11	Sterile	Sterile	
12	Bacillus coli	Bacillus coli	Innumerable
13	Streptococci	Streptococci	
14	Staphylococci	Staphylococci	Few
15	Bacillus coli (many)	Bacillus coli	
16	Sterile	Sterile	
17	Sterile	Sterile	
18	Sterile	Sterile	
19	Staphylococci and Bacillus Welchii	Staphylococci and Bacillus Welchii	1,500 (staphylococci)
20	Sterile	Sterile	
21	Sterile	Sterile	
22	Anaerobic spore former (not Bacillus Welchii)	Sterile	
23	Anaerobic Streptococcus haemolyticus	Anaerobic Streptococcus haemolyticus	
24	Bacillus Welchii	Bacillus coli	100
25	Sterile	Sterile	
26	Few staphylococci	Sterile	
27	Sterile	Sterile	
28	Sterile	Sterile	
29	Streptococci (many)	Streptococci	1,000
30	Bacillus coli	Bacillus coli	
31	Sterile	Sterile	

gallbladders from which it proved impossible to culture bacteria. However, this does not seem to us to be a reasonable assumption, as the percentage of staphylococci found appears to be the same as the figure for several other organisms and, furthermore, it is possible to produce cholecystitis experimentally by the injection of staphylococci.[14] Moreover, in experimental cholecystitis produced by ligating the cystic duct or ligating the cystic artery the staphylococcus is not an uncommon invader along with the other organisms found.[7b] It seems unnecessary, then, to discriminate against this organism any more than against any other found in similar numbers.

The main point is to note the number of instances in which either the bile or the gallbladder wall was sterile. The interpretation of this phenomenon is difficult. Some have regarded the bactericidal powers of the bile as a satisfactory explanation. This appears to us to be

TABLE 6.—*Summary of Data Given in Tables 1 to 5*

Result	Wall		Fluid	
	Number	Percentage	Number	Percentage
Sterile (including diphtheroid bacilli* and Bacillus subtilis)	51	57	61	67
Staphylococci	13	14	8	9
Streptococci	8	9	6	7
Bacillus coli	10	11	14	16
Bacillus Welchii	10	11	8	9
Typhoid bacilli	1	1	1	1

* It may be questionable to ignore diphtheroid bacilli found in such large numbers as 2,600 per cubic centimeter (table 3).

questionable. Bile is certainly not an agent likely to interfere with the growth of organisms of the colon-typhoid group. In fact, it is used in special mediums to favor their growth. Furthermore, there is the well known fact that the typhoid bacillus tends to survive in the gallbladder for many years after the original infection and thus to produce carriers. The bactericidal power of the bile for the cocci is questionable. It is easy to find surviving cocci in the bile in experimental animals for long periods after the organisms have been introduced.[2] This is an observation often recorded. Any one who has tried to preserve pooled specimens of bile or solutions containing bile even when the medium is kept on ice must have noted that organisms of the colon group as well as of the cocci group are present. Magner and Hutcheson[3] have reported that certain cocci grow well in the presence of, while others are killed by, bile.

The medium used was probably one of the best for the growth of cocci, having been especially devised for that purpose, and it is difficult

14. Andrews, E.: Unpublished data.

to see how a fraction of a cubic centimeter of bile when diluted in the whole tube could have much inhibitory power.

Numbers of Bacteria Found.—While one cannot, of course, postulate that the number of organisms found in a given location is indicative of the severity of the infection, the general range of findings in our series does seem significant. When one considers the number of bacteria found per cubic centimeter in the best possible milk it seems strange that in a field such as the gallbladder the flora should be so scant in the presence of varying degrees of inflammation as evidenced by microscopic examination. Cultures of the urine of patients with cystitis or of material from the inflamed appendix are of an entirely different grade. Every field in the microscope shows many organisms. Thus we are at a loss to account for the scantiness of the flora found in the gallbladder.

TABLE 7.—*Percentage of Gallbladders Showing Infection Classified According to Type of Condition*

Type of Condition*	Number of Gallbladders	Wall, Percentage	Fluid Contents, Percentage	50,000+, Percentage
Group 1	8	37	12	0
Group 2	12	50	33	8
Group 3	4	100	100	100
Group 4	36	33	25	8
Group 5	31	42	42	6

* Group 1 comprised normal gallbladders; group 2, normal gallbladders with stones; group 3, gallbladders from patients with obstruction of the common duct, and groups 4 and 5, gallbladders from patients operated on during the active, and during the quiescent, stage of the disease, respectively.

A striking exception is presented by organisms of the colon group. In most cases in which such organisms were found at all they were present in overwhelming numbers. In the dilutions in which the plates were poured it was possible to estimate the number of bacteria up to 50,000; hence the results of cultures described as "innumerable" represent more than that number per cubic centimeter. It would therefore seem much more rational to attribute a causal significance to the colon bacillus than to the coccus group if any bacterial cause is to be considered.

Bacteria Found in Gallbladders of the Various Groups.—One of the greatest discrepancies encountered is the frequent apparent lack of correlation between the bacteriologic observations and the clinical and pathologic data. Table 7 summarizes the observations on the various groups, but it is obvious from a glance at tables 4 and 5 that there is no significant bacteriologic difference between cultures of material obtained during the active and those of material obtained during the

quiescent stage of the disease. Furthermore, histologically the normal gallbladder either with or without stones contains a flora that seems quite comparable both qualitatively and quantitatively to that of gallbladders removed during either the active or the quiescent stage and in which pathologic changes of various degrees have taken place. Especially striking is the comparison between the latter two groups (group 4 and group 5). While any division of such cases may be somewhat arbitrary and several borderline cases may be put into either group, nevertheless the fact remains that, after due allowance for the human equation is taken into account, the numbers of bacteria found in the two groups were about the same. In group 5 (gallbladders from patients operated on in the quiescent stage) bacteria were found in the wall in 33, and in the fluid contents in 25 per cent, of the specimens, whereas in group 4 (gallbladders from patients operated on in the active stage) 42 per cent yielded positive cultures from the wall, and the figure for the bile was the same. In group 5 as well as in group 2 (normal gallbladders with stones) 8 per cent of the specimens showed high bacterial counts in the bile, while in group 4 only 6 per cent of the gallbladders did. Many specimens in the latter group were from patients operated on during severe attacks of acute cholecystitis, and all were obtained at operations performed within a few days after the colic was over and while the gallbladder still presented definite signs of activity.

Gallbladders Showing Large Numbers of Bacteria.—In ten cases in our series there were overwhelming numbers of bacteria in the counts. In 9 of these the organisms were Bacillus coli, and in one, Streptococcus viridans. It is interesting to note first that all the gallbladders from patients with high grade obstruction of the common duct yielded rich growths, although the number is too small to mean much. However, one of us [7b] noted previously that ligature of the common duct in the dog, although producing but slight pathologic change, almost invariably caused the development of a rich flora in the bile. The element of stasis together with a favorable action of bile on the growth of the colon bacillus is obviously to be considered. One must, however, remember that the mere presence of bacteria does not necessarily mean that inflammation is taking place. It is well known that the most profound stasis resulting from carcinoma of the pancreas typically does not cause inflammation of the gallbladder but that Courvoisier's law postulates that one may expect to find a thin-walled gallbladder in such cases.

Of the ten gallbladders regarded as heavily infected five were from patients with typical cholecystitis, as shown by histologic examination. However, the remaining five showed no microscopic changes or such

slight alterations that they could be considered practically normal if one remembers Graham's statement that the finding of a few wandering cells in the mucosa is normal.[5] One gallbladder was that of a patient with carcinoma of the pancreas; the gallbladder was not excised, but it appeared normal grossly. Another patient was subjected to cholecystectomy on the evidence of a stone in the gallbladder, but the subsequent course showed that the diagnosis was wrong and that the patient had an abscessed appendix and a suppurative portal thrombophlebitis. The specimen from that patient was unfortunately lost. The other three gallbladders exhibited but minimal change.

It appears, then, that the finding of enormous numbers of bacteria does not necessarily indicate a severe clinical picture, as only half of the gallbladders showed true pathologic changes.

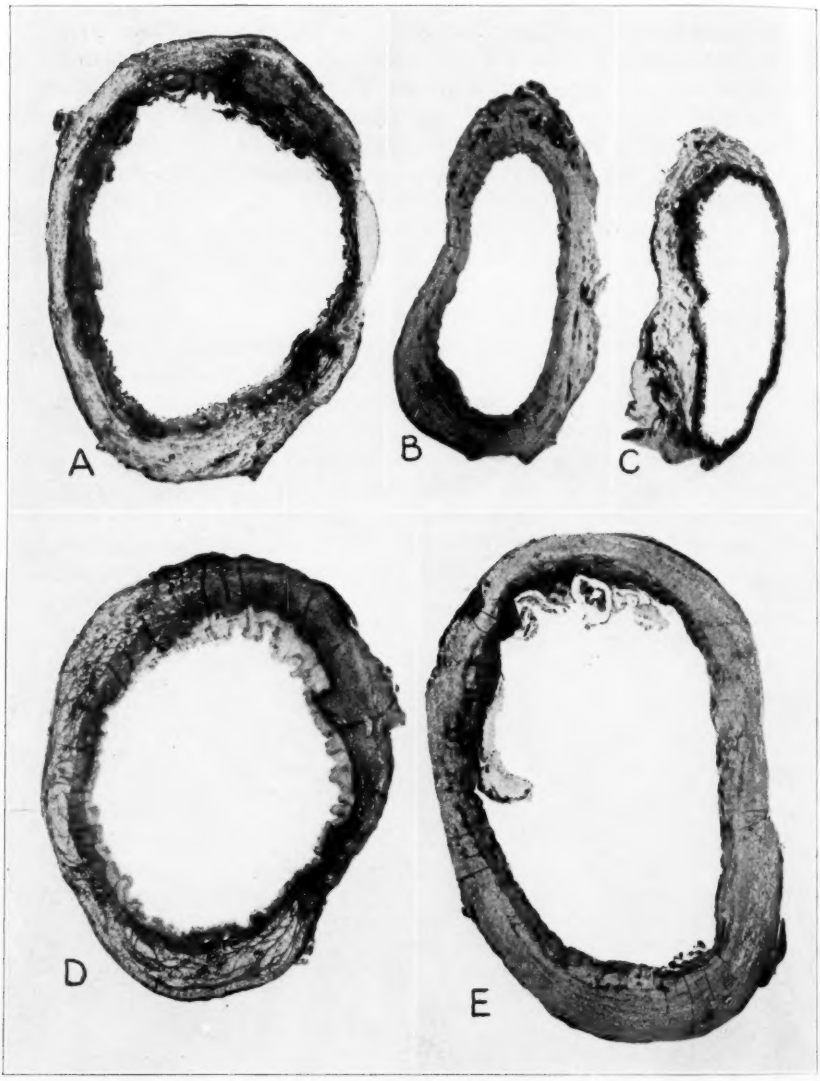
Definitely Damaged Gallbladders with Sterile Contents.—There were sixteen severely damaged gallbladders, all of which for obvious clinical reasons were classified as belonging to group 4. All the patients from whom these specimens were obtained had or had had acute symptoms referable to the gallbladder within a few days before the operation. All the cultures, i. e., from both the wall and the contents, were sterile. In this as in the last group glaring inconsistencies cause one to pause. Six of the specimens showed relatively slight damage to the wall. This is an illustration of the remarkably quick reparative power of the gallbladder, which had been commented on by Boyd.[15] All the other specimens on microscopic examination were found to show changes typical of those of moderate or severe cholecystitis with high grades of pathologic changes in the acute stage. The figure shows photomicrographs of some of these specimens and illustrates the advanced stage of pathologic degeneration encountered. Again one is at a loss to explain the gross lack of correlation between the bacteriologic and the histologic picture and to fit the two together on the assumption that cholecystitis is a disease of purely bacterial origin.

SUMMARY OF OBSERVATIONS

The normal human gallbladder, the undamaged stone-containing gallbladder and the pathologically damaged gallbladder as removed either in the active or in the quiescent stage of the disease contain bacteria in a minority of cases.

The differences between the various flora of different types of gallbladders fall within the limits of chance variation, both qualitatively and quantitatively.

15. Boyd, W.: Surgical Pathology, Philadelphia, W. B. Saunders Company, 1925.



Severe pathologic changes in five gallbladders the walls and fluid contents of which were sterile. Note the extensive thickening and infiltration. Note the marked asymmetry of damage in *C*.

Gallbladders removed during the most acutely active stage of the disease did not yield an appreciably richer flora than other types.

Gallbladders in which a rich flora was found showed no more extensive pathologic changes than did the average specimens in the series.

Conversely, in gallbladders in which extensive histologic evidence of damage was present the flora was no richer than in the average specimen.

An actual majority of the most severely damaged gallbladders were sterile.

The colon bacillus was the only organism that occurred in large numbers. With a single exception the cocci were few in bacterial counts.

COMMENT

The results of our studies as summarized can be interpreted in four different ways, namely: 1. Our cultural methods are at fault. 2. The disease is caused by some unknown organism or virus. 3. The organisms present have been killed by "stewing" in their own juice. 4. Bacteria play but a minor or secondary rôle in disease of the gallbladder.

1. *Faulty Cultural Methods.*—This possibility has been discussed earlier in the paper, and we believe that the answer is "no." Our results are quite in accord with nearly all previous results as to the number of specimens which proved sterile. Even the most enthusiastic advocates of any particular organism as the etiologic agent have uniformly failed to find that organism in more than a minority of cases. Beginning with investigations made by Welch, who found Bacillus Welchii occasionally in bile, many such studies have been made by competent bacteriologists in many countries, and the results have been uniformly of the same order as ours, although there has been some variation in detail. In all investigations the same general flora was found and the incidence of the organisms was within the same range; also half or two thirds of the cultures yielded no bacteria at all. The overwhelming literature in this field cannot be reviewed here, but summarizing articles by Magner and Hutcheson [3] in English and by Seeber [16] and Löwenberg and Meyer [17] in German may be referred to (table 8). One hesitates to accuse a whole generation of bacteriologists of incompetence.

16. Seeber, F.: Klinische und bacteriologische Untersuchungen bei Erkrankungen der Gallenwege, Deutsches Arch. f. klin. Med. **167**:186, 1930.

17. Löwenberg, W., and Meyer, W.: Enterococcus Infections of the Gallbladder, Elective Localization of Pathogenic Microbes, Klin. Wchnschr. **5**:989, 1926.

2. *Unknown Organism or Virus as Cause of the Disease.*—While this, of course, cannot be denied categorically, the hypothesis is not in accord with the usual expectation in cases of abdominal inflammation. Lesions of the colon, appendix, urinary bladder, pancreas, kidney and female genitalia are all caused by combinations of mechanical or vascular insults, often complicated by infection, or by infection alone. In all cases the known bacterial flora has proved ample to explain the conditions found.

TABLE 8.—*Cultures from Gallbladders* [3]

	Number	Positive, per Cent	Strepto-cocci, per Cent	B. Coli, per Cent	Staph-ylococci, per Cent	B. Welchii, per Cent	Other Bacteria, per Cent
1932, Authors, present series							
Fluid contents	106	33	6.5	17.9	4.7	....	5.6
Wall	200	89	29.5	26	26	1	18
1928, Wilkie							
Fluid contents	50	12	4	6	....	2	....
Wall	50	12	4	6	....	2	....
1930, Gordon-Taylor and Whitby							
Fluid contents	50	32	8	12	....	6	6
Wall	50	82	22	18	....	16	26
1929, Branch							
Fluid contents	210	40	15	50	18	5	9
Wall	210	53	11	49	17	8	10
1928, Friesleben							
Fluid contents	132	47	11	28	....	....	8
Wall	96	76	13.5	28	32	....	2
1927, Illingsworth							
Fluid contents	100	40	17	21	3	....	....
Wall	100	62	39	22	....	....	6
1927, Judd, Mentzer and Parkhill							
Fluid contents	193	14.5	8	6	1	0.5	4
Wall	200	49	18	4.5	10	1	20
1916, Rosenow							
Fluid contents	29	55	17	31	....	....	24
Wall	32	84	56	28	....	22	22
1925, Johnson							
Fluid contents	100	32	3	18	7	....	4
1924, Blalock							
Fluid contents	270	58	5	31	....	....	10.7
1922, Drennan							
Fluid contents	100	19	2	12	4	....	1
Average of results							
Fluid contents	1,340	34.7	8.7	21			
Wall	938	63.4	24	22.6			

3. *Destruction of Organisms "Stewing" in Their Own Juice.*—It is well known that in many cases of acute infection there are stages of the disease in which the in vitro cultivation of bacteria is impossible. The finding of sterile pus is not surprising to any surgeon or bacteriologist even in cases in which smears show many bacteria. Classic examples of this are empyema of the chest and tubo-ovarian and appendical abscess. There are, however, marked objections to this hypothesis. First, the gallbladder, even the acutely diseased one, has been found sterile by all students in a proportion of cases far higher

than that obtaining for other inflamed viscera. While sterile pus is not a rarity in other diseases, it is decidedly exceptional, and one would not expect to find it in an actual majority of cases. We feel sure that any surgeon who was told by his laboratory staff that pus was sterile in two thirds of his cases would soon start an investigation as to the competence of that staff. Second, the presence of sterile pus is a definite stage in many diseases. It occurs after the acute infection is over, the host has built up antibodies and time has elapsed for the development of enough growth products to kill the bacteria. In disease of the gallbladder the observations are quite different. Bacteria are present or absent in about equal numbers at all stages of the process, which is quite a different matter from the nontuberculous "cold abscess" and is not in any way comparable to it.

4. *Minor or Secondary Rôle Played by Bacteria in Disease of the Gallbladder.*—Before the rôle of bacteria can be adequately considered, one must examine the question of whether or not there is a normal flora of the gallbladder. Our own cultures of normal gallbladders, of normal gallbladders containing stones as well as of specimens obtained during the quiescent stage of the disease indicate that there is such a flora and that it is comparable in degree and kind with that found in actively diseased gallbladders.

The presence of bacteria in normal gallbladders is not by any means a new observation. Osler [4] noted the fact that in cases of typhoid fever large numbers of typhoid bacilli were almost uniformly found in the bile, in spite of the fact that cholecystitis was a comparatively rare complication, having been found by him in only 19 of 1,500 cases of typhoid fever. Furthermore, it is well known that in cases of bacteremia from many causes, although many organisms find their way into the bile, the occurrence of cholecystitis is rare. Cultures of human bile taken post mortem have long been known to be positive, but this observation has generally been ignored as it was thought that agonal or postmortem changes were a sufficient explanation. However, there has been a gradual accumulation of other facts that seem to lead to a different interpretation. It has been observed in experimental animals that the gallbladder contains bacteria in a high percentage of cases. Walsh and Ivy [18] found this quite uniformly. One of us [7b] made similar observations, although he found dogs' bile to be sterile in most cases while the wall of the gallbladder contained bacteria, and Ivy found bacteria in the bile itself frequently. Probably the general con-

18. Walsh, E. L., and Ivy, A. C.: The Etiology of Gallstones, Ann. Int. Med. **4**:134, 1930.

dition of the animals, as well as the diet and the temperature of the cages, has considerable influence. Recent work by Graham has shown the intimate association between the lymphatics of the gallbladder and those that drain the bowel, and besides it has long been known that the liver receives some of the portal lymph drainage through this network. Zinsser [19] noted that a considerable range of intestinal flora is carried to the liver and destroyed. In his book on infection and immunity he called attention to the fact that bacteria frequently lie dormant in the tissues and cause no infection unless other damage to the tissue is produced. He quoted the experiments of Tarozzi, who injected tetanus spores into the portal circulation. These were carried to the liver and lay dormant for as long as fifty days. Trauma of animals into whose circulation tetanus spores had been injected caused tetanus.

The experiments of Arnold [20] are pertinent. He showed that during certain stages of normal digestion in the dog the permeability of the duodenum is so great that as many as 1,000 bacteria per cubic centimeter can be plated from a cervical lymphatic fistula. Normally, of course, these are destroyed by elements of the reticulo-endothelial system, especially by the Kupffer cells of the liver. Ellis and Dragstedt [6] found that a spore-forming anaerobe is a constant inhabitant of the livers of dogs. Andrews and Hrdina [7a] showed that this is a true Welch bacillus and found that it can be isolated from dogs' muscle as well. In their animals it was present in small numbers and generally was not recovered in cultures made by simply swabbing the cut surface. On the other hand, if the material was first incubated for twenty-four hours, the foul odor and rapid formation of explosive gas in cultures failed only once in over one hundred experiments. Experiments [8] in which a dog's leg was ligated tightly with wire showed that not only gangrene but actually gas gangrene occurred as a rule. Blood-borne or exogenous infection seems to be ruled out. The identification of this organism by Wolbach and Saiki [21] was first made in 1909 and has been confirmed in many laboratories. Recent denial of its identity with the true Welch bacillus on immunologic grounds by Trusler and Reeves [22] does not conform to the usual accepted bacteriologic standards.

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19. Zinsser, Hans: Infection and Resistance, New York, The Macmillan Company, 1923.

20. Arnold, L.: Alterations in the Endogenous Bacterial Flora and Microbic Permeability of the Intestinal Wall, J. Hyg. **29**:82, 1930.

21. Wolbach, S. B., and Saiki, T.: A New Anaerobic Spore Bearing Bacterium Commonly Present in the Livers of Healthy Dogs, J. M. Research **21**:267, 1909.

22. Trusler, H. M., and Reeves, J. B.: The Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, Arch. Surg. **28**:479 (March) 1934.

As shown by Judd and his associates,[23] its pathogenicity is low, and our own experience has been that not only anaerobes but a large section of the usual intestinal flora are present. The anaerobes have received more prominence because they are hardier, spore-forming bacteria while the others are easily killed (David and Loring[24]). Human livers examined at autopsy showed the same flora as that present in the livers of dogs. The usual question as to whether the flora found at autopsy is an agonal one is hard to answer. In order to rule out this factor we have been trying to obtain livers from patients who died suddenly. Thus far seven specimens have been examined, all of which yielded positive cultures.

The mere presence of the gallbladder in such a field suggests that it would be unusual in the highest degree if it did not occasionally share the flora of the adjacent liver. How many of the organisms pass into its lumen or enter it through the cystic duct is problematic, but that a few may frequently do so has been the universal experience of chemists who have tried to study bile. Bile affords such an ideal culture ground for many types of bacteria that chemical studies of pooled bile have always been handicapped by the fact that it is practically impossible to secure sterile specimens of bile either from man or from animals. Even bile withdrawn under the most careful aseptic precautions rapidly undergoes bacterial decomposition and must be sterilized by heat or addition of alcohol. This fact, quite familiar to all who have worked in this line, is indicative of a normal biliary flora.

The association of disease of the gallbladder with infection has in many ways been a rather forced one. The experimental production of cholecystitis by many types of virulently pathogenic organisms is no proof whatever that this process goes on in man. It is obvious that members of the coccus group or the colon bacillus group incite suppuration wherever placed in the body. When one considers that organisms injected intravenously tend to lodge in the liver and hence get into the bile naturally, it is obvious that some reaction may take place. Nevertheless, acute cholecystitis as it occurs in man has never been produced in that manner. The enormous thickening and induration of the wall, the swelling with closure of the cystic duct and the general picture surgeons know so well is not reproduced. All that can be found even after injections of overwhelming numbers of organisms is a slight to moderate cellular infiltration of the walls. On the other hand, Peter-

23. Thorsness, E. T.: Bacteriology of Cholecystitis, Surg., Gynec. & Obst. **59**:752, 1934.

24. David, V. C., and Loring, M.: The Rôle of the Welch Bacillus in Experimental Peritonitis, Arch. Surg. **26**:1103 (June) 1933.

man and Graham,[25] Cushing,[26] Meyer and his co-workers [27] and many others have pointed out that in order to produce experimental cholecystitis with any regularity it is necessary to damage the viscus or interfere with its blood supply. Especially striking are the results of Peterman and Graham,[25] who injected large numbers of virulent colon bacilli into the gallbladder through the cystic duct with no resulting infection. Equally striking is the fact that just as typical inflammatory reactions may be produced by means other than bacteria. Ivy noted the great susceptibility of the dog's gallbladder to infection after trauma. One of us [7b] produced typical changes both histologically and bacteriologically by ligating the cystic duct. The mere insertion of a needle into the gallbladder of a dog frequently stirs up an inflammatory reaction quite as typical as that produced by bacteria.

Furthermore, histologic investigation [28] of diseased gallbladders does not lend support to the infective theory. This point has been emphasized recently by Feinblatt.[29] His studies gave the same results as our own. The chief factors in the pathologic picture are edema, hemorrhage and infiltration by round cells. Pus cells are few, even in many acute cases. These points seem to fit better with mechanical or vascular insults than with infection alone. Feinblatt examined smears from twenty gallbladders with empyema and found that the material which resembled pus contained few leukocytes. In the majority of the cases the material was sterile on culture. Our own observations indicate that there is no increase in the number of leukocytes present in bile from diseased gallbladders.[29]

Seeber's [16] results are even more striking. In the series reported by him about half of the gallbladders were sterile. Those from febrile patients showed B. coli in about twice the number that those from afebrile ones did. Nevertheless one fourth of the gallbladders from febrile patients were sterile.

Since the results of our studies tend to minimize the importance of bacteria, one must search for other causes. Some progress has already been made along this line. An example of pancreatic apoplexy which we observed causes one to suspect the entrance of chemically

25. Peterman and Graham, cited by Graham.[13]

26. Cushing, H., quoted by Meyer et al.[27]

27. Meyer, K. F.; Nelson, N. M., and Fensier, M. L.: Mechanism of Gallbladder Infection in the Laboratory Animals, J. Infect. Dis. **28**:456, 1921.

28. Andrews, E.: Detailed Studies of a Series of Gall-Bladder Cases, Surg., Gynec. & Obst. **57**:23, 1933.

29. Feinblatt, H. M.: The Infrequency of Primary Infection in Gall-Bladder Disease, New England J. Med. **199**:1073, 1928.

toxic material in a retrograde manner. Wolfer [30] has shown that pancreatic juice sets up a moderate degree of inflammation in the gallbladder. This observation has been confirmed by Andrews, Goff and Hrdina.[31] Gastric juice is even more toxic than pancreatic juice, and intestinal contents are of about the same grade of toxicity (Andrews). Even more striking is the proof by Mann [32] that chemicals may be excreted in such amounts in the bile that typical inflammatory changes are produced in the gallbladder. Chlorine administered intravenously as surgical solution of chlorinated soda sets up such a syndrome, in which the most prominent pathologic feature is edema characteristic of human acute cholecystitis (figure). Furthermore, Copher, Glover and Kendall [33] have also produced cholecystitis by the intravenous injection of material derived from obstructed loops of intestine. Again edema was marked.

A recent suggestion by one of us may be added. In line with the view that gastric ulcer is undoubtedly caused by the corrosive power of the acid juice, one cannot afford to overlook the possibility that a similar mechanism may be at work in the gallbladder. Demonstrations by Dragstedt, Mann and others that pure gastric juice has the power to produce ulcers with great regularity in isolated segments of the stomach make one wonder why equal consideration cannot be given to the bile. It contains a substance, bile salts, the toxicity of which is quite comparable to that of hydrochloric acid. These salts are concentrated in the gallbladder to the enormous degree that they may reach 10 per cent strength (Hammarsten [34]), although most of our own observations fall short of this figure. Solutions of this strength have been shown by Rewbridge and Hrdina [35] to be capable of causing fatal peritonitis, myositis or pneumonitis. Pancreatitis with fat necrosis was also observed by Rewbridge.[36] Thus there may occur the apparently

30. Wolfer, J. A.: Rôle of Pancreatic Juice in the Production of Gallbladder Disease, Surg., Gynec. & Obst. **53**:433, 1931.

31. Andrews, E.; Goff, M., and Hrdina, L.: Effect of Pancreatic Juice on the Absorptive Mechanism of the Gall-Bladder, Proc. Soc. Exper. Biol. & Med. **29**: 1091, 1932.

32. Mann, F. C.: Production by Chemical Means of a Specific Cholecystitis, Ann. Surg. **73**:54, 1921.

33. Copher, Glover H., and Kendall, quoted by Graham.[13]

34. Hammarsten, O.: Textbook of Physiological Chemistry, New York, John Wiley & Sons, Inc., 1911.

35. Rewbridge, A. G., and Hrdina, L.: Etiological Rôle of Bacteria in Bile Peritonitis, Proc. Soc. Exper. Biol. & Med. **27**:528, 1930.

36. Rewbridge, A. G.: Fat Necrosis in Bile Peritonitis, Arch. Path. **12**:70 (July) 1931.

paradoxical train of events that too strong a concentration of the solvent (bile salts) provokes an inflammation capable of producing absorption and hence precipitation of the cholesterol held in solution by them.

CONCLUSION

The results of our studies suggest that bacteria may play but a secondary rôle in disease of the gallbladder and that other possible factors, mechanical, vascular, toxic and chemical, deserve more careful study.

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART V

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TUBERCULOSIS OF THE PULMONARY VESSELS

Tuberculosis of the pulmonary vessels is probably always present in cases of phthisis. The process affects successively the adventitia, media and intima of vessels in the walls of tuberculous cavities. The wall of the vessel may bulge, giving rise to the aneurysms of Rasmussen, which may burst and cause severe hemoptysis. Usually this is prevented by the occurrence of thrombosis. The erosion of a caseous gland into a pulmonary vein and the discharge of its contents into the lumen constitute a well known cause of miliary tuberculosis. Occasionally, isolated tuberculous vegetations occur in the intima of large pulmonary arteries and veins.[x]

In the present series pulmonary tuberculosis was present in 6 patients and all showed tuberculosis of the pulmonary vessels. Arteries and veins of all sizes were affected, but involvement of the small vessels was commonest.

1. LARGE ELASTIC ARTERIES

In a woman of 65 with chronic, relatively inactive fibrocaseous tuberculosis with cavitation of the upper lobe of the right lung, an artery 2.2 mm. in diameter was involved. Its intima was normal. The whole thickness of the media in two long stretches was completely necrotic. The adventitia adjacent to these areas showed rather inactive tuberculosis, with much fibrosis and some caseation and calcification. This was continuous with a large fibrocaseous patch in the adjacent lung tissue. It is noteworthy that although the caseous process was separated from the lumen of the artery only by the internal elastic lamina and a layer of endothelium, there was no overlying thrombosis. A slight extension of the lesion would have caused the artery to burst.

In this case several small veins also were involved.

In this series of five papers the superior numbers refer to the bibliography which is printed at the end of this paper. The superior letters refer to footnotes.

(*x*) 122, 138.

2. SMALL MUSCULAR ARTERIES

The small muscular arteries were involved in 5 cases. The affected vessels were always near tuberculous foci in the lungs. The commonest lesion was endarteritis obliterans. The lumen was greatly narrowed or completely obliterated by loose fibrillar connective tissue containing many lymphocytes, large mononuclears and occasionally tuberculous giant cells. Capillary lumens also were often present. In a case in which there were dense old scars at the apexes of the lungs the small arteries in the scars showed an intima consisting of thick, dense connective tissue greatly narrowing or obliterating the lumen, apart from a few recanalizing lumens. The media in some of these arteries was replaced by dense hyaline connective tissue over long stretches. In the other cases it was occasionally normal but usually showed infiltration with cells similar to those in the intima, and often on the side next to the tuberculous focus in the lungs it showed caseation with complete loss of structure. Sometimes when an artery was traced into a tuberculous focus in the lung and before the caseous mass was reached, the lumen was occluded by tuberculous granulation tissue, while the media was still normal. When the caseous mass was reached the internal and external elastic laminae frayed out and disappeared, and finally the artery was lost as it merged with the caseous mass. Changes such as these were observed in only a few arteries in each of the 5 cases. They were never widespread enough to cause obstruction to the pulmonary circulation.

3. SMALL VEINS

The small veins were involved in 3 cases. In all of them the intima showed thickening by loose fibrillar connective tissue containing many lymphocytes, large mononuclears and polymorphonuclears and occasionally a few capillary lumens. Usually there was a similar process in the media and adventitia, the whole thick wall of the vein then consisting of loose cellular, vascular connective tissue. Sometimes the portion of the wall adjacent to the tuberculous focus in the lung was caseous.

4. LARGE INTRAPULMONARY VEINS

The large intrapulmonary veins were involved in only 1 case. The intima of veins near tuberculous foci showed patchy thickening by loose cellular connective tissue containing capillary lumens. The media showed a similar but less extensive process. The adventitia consisted of dense vascular connective tissue showing some infiltration with lymphocytes and large mononuclears.

RHEUMATISM OF THE PULMONARY ARTERIES

Attention has recently been drawn to the widespread lesions in blood vessels occurring in the course of acute rheumatism. Little clinical

importance has been attached to these, though Swift [293] attributed the common cardiac pain in cases of rheumatic cardiac disease to involvement of the arteries, particularly the aorta; Slater [280] reported 3 cases of occlusion of the coronary artery in the course of rheumatic fever, and Neale [218] described 2 cases of rupture of the aorta in the course of acute rheumatism. Two cases of rheumatism of the pulmonary arteries were observed in the present series.

CASE 1.—H. C., a man aged 39, died of congestive heart failure due to rheumatic cardiac disease with mitral stenosis and auricular fibrillation. At autopsy the usual signs of chronic venous congestion were observed. The heart weighed 525 Gm. All the chambers were dilated, and the left auricle and right ventricle were hypertrophied. The mitral valve showed extreme stenosis, and there were slight old changes in the aortic valve also. In addition there were recent vegetations on the mitral, aortic and pulmonary cusps. The pulmonary arteries were somewhat dilated and showed marked atherosclerosis. An adherent thrombus was present in the main branches to the right lower and middle lobes.

Microscopically the stem of the pulmonary artery showed moderate atherosclerosis. The main branches to the right and left lungs (fig. 31) showed a great deal of atherosclerosis, the intima being 0.83 mm. thick, compared with a thickness of from 0.25 to 0.33 mm. for the media. The adventitia consisted of dense fibrous tissue. Many of the vasa vasorum were almost occluded by cellular intimal thickening, and around them was much infiltration with large mononuclears, lymphocytes and fibroblasts. The media in several long stretches showed ingrowth from the adventitia of many capillaries, young connective tissue and many round cells. There the elastic laminae and muscle were interrupted and destroyed, sometimes in the whole thickness of the media. In other areas the portion of the media immediately beneath the intima was swollen and degenerate, consisting of fibrous tissue with a few shrunken muscle cells and a few short irregular elastic fibers. The intima consisted of dense fibrous tissue with a little calcification near the surface. There were many spindle cells and small groups of fat-containing foam cells. Over the damaged part of the media the round cell infiltration spread into the deeper parts of the intima. No other rheumatic changes were observed in the lungs or in the vessels of any other organ.

CASE 2.—I. B., a woman aged 26, died of congestive heart failure due to rheumatic cardiac disease with mitral stenosis and incompetence. At autopsy the usual signs of chronic venous congestion were observed. The heart weighed 750 Gm. The pericardium was universally adherent to the surface of the heart. There were great dilatation of all the cavities and hypertrophy of both ventricles, especially the right. The mitral cusps showed great old sclerosis with shortening and thickening of the chordae tendineae, but the fibrous ring surrounding the valve was dilated. There was slight old sclerosis of the aortic and tricuspid cusps. Recent vegetations were present on the mitral, tricuspid and pulmonary cusps. The pulmonary arteries were dilated and showed marked atherosclerosis.

Microscopically the stem and large intrapulmonary branches of the pulmonary artery showed fairly marked atheroma. Many of the large branches (fig. 32) also showed large or small patches of endothelial hyperplasia, forming large polypoid masses of large oval or spindle-shaped cells with vesicular nuclei, projecting into the lumen. A few red blood cells and many large mononuclears and lymphocytes and a few polymorphonuclears were entangled in the mass, and the underlying intima often showed infiltration with similar cells. The media and

adventitia were normal apart from intimal thickening of some of the vasa vasorum. The largest endothelial mass seen, in an artery 1.1 mm. in external diameter (lumen, 0.7 mm.), was 1.7 mm. in diamter at its base and projected for 0.4 mm. into the lumen. The main veins in this case also showed infiltration with lymphocytes and large mononuclears in all three coats. This was also possibly a rheumatic change.

LARGE ARTERIES

Changes in large arteries are probably common. Kugel [152] noted gross changes in 2 of 24 cases of acute rheumatic carditis and microscopic

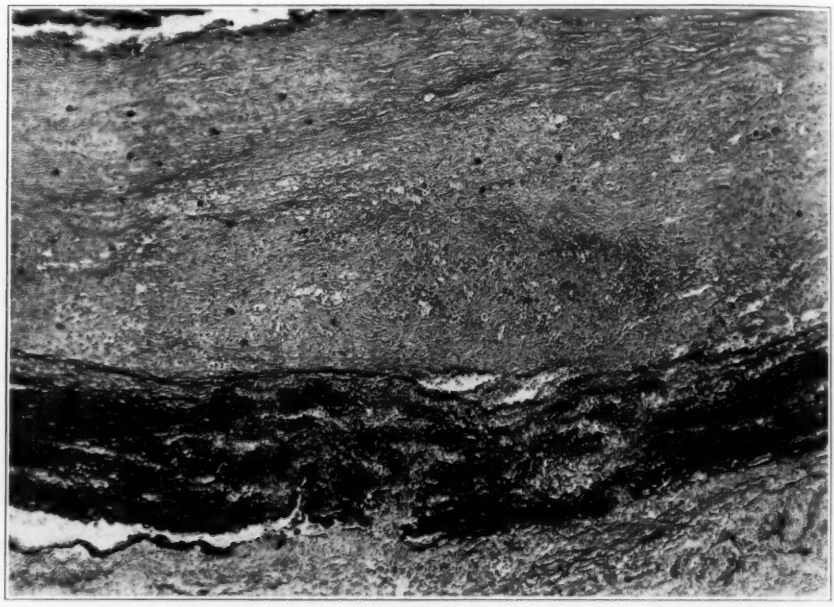

Fig. 31.—Photomicrograph of a section of a pulmonary artery to the right lung showing rheumatic arteritis (× 84; stained with Verhoeff's elastic tissue stain and Van Gieson's stain). There is invasion of the media by new vessels, young connective tissue and many round cells and disruption of the elastic laminae. Great intimal thickening is seen with some round cell infiltration.

changes in 17. In the acute stage the lesions appeared as small, irregular grayish-yellow or brown patches, different from the surrounding atherosclerotic plaques.[y] In the chronic stage there was a rippling or pitting of the intima[z] with thinning of the underlying media. Gray [120] observed a dissecting aneurysm of the pulmonary artery in

(*y*) 152, 222.
(*z*) 55, 120.

1 of his cases, and Neale [218] described 2 cases of rupture of the aorta. Microscopically, sometimes Aschoff nodules were seen in the adventitia,[a] but more usually there was a fairly diffuse round cell infiltration of the adventitia, often most marked around the vasa, which frequently showed endarteritis obliterans. The infiltration, as in case 1, spread into the media, destroying the elastic laminae and muscle. The intima sometimes escaped but often showed round cell infiltration, at times surrounding areas of collagenous necrosis. Pappenheimer [222] described this type of

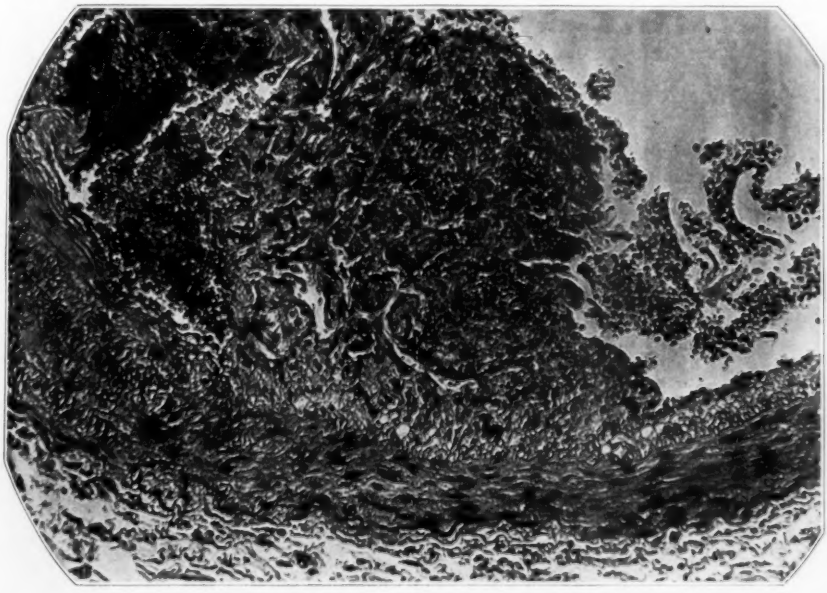

Fig. 32.—Photomicrograph of a section of a large intrapulmonary artery showing rheumatic arteritis (× 146; stained with methylene blue and eosin). There is great patchy proliferation of the intimal endothelium.

lesion as the result of invasion from the lumen of the artery rather than of spread from the adventitia.

In the healed stage there were perivascular fibrous scars in the media, or sometimes large scarred areas interrupting the elastic laminae.

The lesions were strikingly similar to those seen in cases of syphilitic mesarteritis, and, notwithstanding the statement of Pappenheimer [222] to the contrary, the cellular infiltration and destruction of medial elastic tissue sometimes were as great as in that condition. Caussade [53] described the case of a patient with mitral stenosis with a negative Wassermann

(*a*) 152, 222, 229, 230.

reaction in whom such lesions were observed as a case of "arterite syphilitique pulmonaire chez un cardiaque noir," and perhaps similar mistakes are commonly made. There are three chief differences between rheumatic and syphilitic arteritis: 1. Many of the cells are large with one or occasionally more nuclei, though as in cases of syphilis there may also be many lymphocytes and plasma cells. 2. The lesion commonly extends to the intima. In cases of syphilis the only change in the intima is a reactive acellular fibrosis. 3. Aschoff nodules or great endothelial proliferation of the intima of the vasa vasorum in the adventitia are sometimes observed in cases of rheumatic disease.

In view of the frequency and severity of the lesions, it is remarkable that serious consequences do not frequently follow, though 1 case of dissecting aneurysm of the pulmonary artery [120] and 2 cases of rupture of the aorta [218] in which similar lesions occurred have been described. True rheumatic aneurysms are exceedingly rare, though the dynamic dilatation of the aorta and pulmonary artery seen in the roentgenograms in cases of rheumatic cardiac disease have been attributed to these changes.[55]

MEDIUM-SIZED ARTERIES

In arteries from 1 to 10 mm. in diameter Gouley [119] described endothelial proliferation which almost occluded the lumen and which was similar to that in case 2. In somewhat larger vessels in addition to this there sometimes were lesions in the media similar to those in the large arteries. That is almost the only reference to rheumatic lesions in medium-sized pulmonary arteries, though Pappenheimer [222] said that in systemic arteries of that size there may be cellular infiltration of the intima, sometimes with polymorphonuclear infiltration of the media.

SMALL ARTERIES

Small arteries are said to be involved in from 20 to 40 per cent of cases of acute rheumatism.[229] Similar changes also occur in the small systemic arteries.[224] The wall of the vessel is necrotic, and it and the surrounding tissues are infiltrated with fibrin and surrounded by an infiltration of polymorphonuclears, large mononuclears, lymphocytes and plasma cells. There may be extravasation of blood into the wall of the vessel. When healing occurs, new capillaries grow in from the adventitia, and the lumen becomes greatly narrowed by the development inside the elastica interna of a thick layer of loose cellular vascular connective tissue resembling an organized thrombus. Brenner [43] described a case of mitral stenosis in which many of the small pulmonary arteries showed great intimal thickening by cellular connective tissue, often with reduplication of the elastica interna, but he concluded that the endarteritis obliterans was probably a reaction to the chronic (possibly rheumatic)

pneumonic process in the lung tissue and was not due directly to rheumatism. It is possible that such lesions, if widespread, may help to embarrass further an already damaged heart.

CAPILLARIES AND VENULES

The capillaries and venules were sometimes involved in the necrotic process described by Pappenheimer [222] and ruptured readily. That may be the cause of the early hemoptysis noted in cases of rheumatic cardiac disease.

SEPTIC INFLAMMATION OF THE PULMONARY VESSELS

Acute and subacute infections of the pulmonary arteries and veins are common but are usually merely incidents in an infective illness that is fatal in itself. The cases may be classified according to the manner in which the infection reaches the pulmonary vessels:

MODE OF INVASION

I. *Spread by Continuity from Infective Endocarditis of the Pulmonary Valve.*—No examples of this were found in the present series, but it has been described in cases of pulmonary infective endocarditis due to the gonococcus, pneumococcus or influenza bacillus.[b] The ulceration spreads from the cusps of the valve for a variable distance up the pulmonary artery. Microscopically the intima is seen to be replaced by fibrin and leukocytes, and there is polymorphonuclear infiltration of the underlying media, with areas of partial repair, as shown by the presence of cellular vascular scars.

II. *Invasion from Without by Direct Spread from an Infective Process in the Surrounding Tissues.*—This is much commoner and occurred in 4 cases in the present series. In 2 there was a chronic pulmonary abscess and in the others chronic pneumonia, associated in 1 case with bronchiectasis. Several vessels were involved in each case. In 2 the small arteries and in 3 the small veins were affected.

A. Arteries: In 1 case many small arteries showed a thick intima consisting of loose connective tissue infiltrated with lymphocytes and polymorphonuclears. There was slighter cellular infiltration of the media and adventitia. In the other case there was dense lymphoid infiltration of the adventitia, penetrating into the media but not into the intima. In each case all the affected vessels were either near a large chronic pulmonary abscess or in areas of chronic pneumonia surrounding bronchiectatic cavities.

B. Veins: The affected veins had an external diameter of from 0.4 to 0.5 mm. and were always in chronic pneumonic areas or near

(*b*) 201, 294.

the wall of a chronic pulmonary abscess. In 1 case small bronchial veins were similarly affected. The intima was considerably thickened. It consisted of loose connective tissue, sometimes with a number of capillary lumens, and contained many lymphocytes and sometimes large mononuclears and polymorphonuclears. The media and adventitia showed similar round cell infiltration less frequently, possibly because when the lesion reached the intima it spread horizontally along it. Such changes make it easy to understand why secondary abscesses in the brain are so common in cases of bronchiectasis and abscess of the lung.

In no case in the present series were the large pulmonary vessels invaded from without, but Boswell [39] described a case in which infection spread to the main right pulmonary artery from an inflamed mediastinal lymph gland with which it was in contact. Death was due to occlusion of the affected portion of the artery by a thrombus.

III. *Invasion Through the Vasa Vasorum.*—This is rare but probably occurs occasionally in cases of pyemia in which the infection has gained access to the systemic circulation. Mehlin [201] described a case in which there was an abscess in the media of the stem of the pulmonary artery with much less polymorphonuclear infiltration of the intima and adventitia. A somewhat similar case (that of a man who died of pyemia after prostatectomy) occurred in the present series. There were many septic emboli in the pulmonary arteries, but several arteries containing no such emboli showed extensive polymorphonuclear infiltration of the media which destroyed the muscle and separated the elastic laminae but produced only minor changes in the intima and adventitia. In these cases though spread through the vasa vasorum was a possibility, it is much more probable that the infection reached the arteries from infected emboli in the lumen and for some reason spread more widely in the media than elsewhere.

IV. *Infection Reaching Pulmonary Vessels from Their Lumens.*—*A.* Spread from an Infected Embolus: This is common, and 3 cases were noted in the present series. In 2 cases only large vessels were involved. The lumens contained clots infiltrated with polymorphonuclears. There was polymorphonuclear infiltration of the underlying intima and often more intense and widespread infiltration of the media with separation but not destruction of the elastic laminae. There was usually also some polymorphonuclear infiltration of the adventitia. In the third case (that of a man who died of sepsis after prostatectomy) many small muscular arteries contained thrombi in various stages of organization, in which were many polymorphonuclears and large mononuclears. There were many polymorphonuclears in the underlying thickened intima but none in the media. In a fourth case (that of a woman who died of pulmonary embolism after removal of the ovaries and tubes)

syphilitic aortitis was observed at autopsy. Many large pulmonary arteries were blocked by laminated, nonadherent, apparently uninfected thrombi. The right main pulmonary artery showed great thickening of the adventitia, which contained many fibroblasts, large mononuclears and capillaries with a swollen endothelium. Many of the thrombosed arteries and some without thrombi showed a similar subacute adventitial lesion, and others showed a more acute lesion, with an exudation of fibrin, red blood cells and some leukocytes and with collections of large mononuclears in the surrounding connective tissue. The lesion in the adventitia usually appeared older than the thrombi in the lumen, which were unorganized and not septic. The possibility that there may be a primary adventitial lesion (perhaps syphilitic) with secondary thrombosis must be considered. But organization of thrombi in large arteries may be long delayed, and perhaps the presence of thrombi in the lumen excites a reactive inflammatory lesion in the adventitia.

B. Direct Implantation of Infection in the Intima Without Preceding Embolism: Most of the cases that have been reported in the literature were of this type, but no such case occurred in the present series. The cases may be subdivided according to the presence or absence of special strain on the pulmonary arteries which predisposes them to infection.

In the following cases there was no special strain on the pulmonary arteries, but infection usually occurred in the course of an acute specific fever.

(*a*) In cases of influenza Obendorfer [220] and Corten [61] said that the primary lesion is necrosis of the small pulmonary vessels with thrombosis followed by suppurative arteritis and hemorrhages into the surrounding lung tissue. The hemorrhages then become secondarily infected, and sepsis dominates the clinical and pathologic picture. Others [37] have expressed the belief that suppurative pneumonia is primary and that the vascular lesions are secondary.

(*b*) A case of gonorrhea was described by Fürth [110] in which septicemia and multiple pulmonary embolisms followed gonorrhea, and the patient died of congestive heart failure. At autopsy no evidences of infective endocarditis were found. There was a partly organized, infected thrombus in the stem of the pulmonary artery. Fürth said that he thought that the primary lesion was gonococcic endarteritis with secondary thrombosis, but the evidence for this diagnosis seems insufficient.

(*c*) Mehlin,[201] in a boy who died of typhoid, observed extensive acute suppuration in the intima of the stem of the pulmonary artery and a less extensive and a more chronic type of lesion in the media and adventitia.

In most of the cases reported due to direct implantation there was strain on the pulmonary arteries predisposing to infection. The strain may be due to a congenital or an acquired lesion.

The commonest congenital lesion is patent ductus arteriosus.[c] Abbott [1] said that 21 of 92 patients with a patent ductus arteriosus died of infective endarteritis. The signs of infective endocarditis, with special incidence of emboli in the lungs, became superimposed on those of the original congenital defect. The pulmonary artery, its main branches and the patent ductus were filled with a grayish friable clot. There was often secondary infective endocarditis of the pulmonary and tricuspid valves and sometimes a fusiform aneurysm of the pulmonary artery. The clot and the underlying wall of the artery were densely infiltrated with leukocytes. Mehlin [201] described a similar case in which there was an accessory cusp to the pulmonary valve but not a patent ductus. No doubt in these cases the infective endarteritis was primary and the thrombosis secondary.

With regard to acquired lesions, French authors have described acute pulmonary arteritis in cases of mitral stenosis.[d] After an infection, prolonged pyrexia, anemia, cyanosis, dyspnea and repeated hemoptyses occurred and the patient dies in a few weeks of marasmus and asphyxia. In cases in which heart failure is already present when infection occurs, the signs of infection are not clinically obvious, but death soon occurs from rapidly progressive heart failure. At autopsy widespread thrombosis of the pulmonary arteries is often observed. In places not covered by thrombus there are so-called fibrinoleukocytic vegetations on the ulcerated surface of atheromatous patches. These showed beginning organization and contained gram-positive cocci. Such cases have been described only in the French literature. Probably the presence of the cocci is due to agonal invasion of the blood stream and the lesions are really rheumatic.

Comment.—Thus, pulmonary arteritis occurs as a serious complication in a large proportion of cases of patent ductus arteriosus. Its occurrence in cases of acquired cardiac disease is not established, and its importance there is certainly not great. It occurs in every case of pyemia with septic pulmonary emboli but is only an incident in the condition and probably is of little direct importance, though possibly occasionally the affected artery may rupture, causing fatal hemorrhage. Pulmonary arteritis also occurs in all cases of suppurative pulmonary disease, and in these cases involvement of the pulmonary veins may be the cause of metastatic abscesses in the brain and elsewhere.

(*c*) 35, 118, 259, 269.
(*d*) 59, 160, 165, 183.

PERIARTERITIS NODOSA

Periarteritis nodosa is rare in the pulmonary vessels. Sternberg [287] described 1 case and said that only 2 others have been reported. Her patient had been pyrexial for one week, and there were signs of consolidation at the base of the left lung. She died following profuse hemoptysis. At autopsy the lower lobe of the left lung and the left pleura were full of blood. The walls of the small and large pulmonary arteries were necrotic, and they and the surrounding lung tissue were infiltrated with leukocytes. The diagnosis of periarteritis nodosa does not seem to be fully established in this case.

PRIMARY NEOPLASMS

The occurrence of a primary neoplasm of the pulmonary vessels is rare, records of only 2 cases having been found in the literature.[e] Both patients died of congestive heart failure. In the first case, that of a man of 68, the stem of the pulmonary artery was filled by an adherent, dense yellowish mass which spread into the main branches. Microscopically it was a malignant leiomyoma. In the second case, that of a child of 3½ years, there was a simple leiomyoma growing from the left pulmonary vein.

SECONDARY NEOPLASM

Secondary neoplasm of the pulmonary vessels occurs much more frequently and there were 8 examples in the present series. The tumor may reach the pulmonary vessels either by embolism or by invasion from without.

TUMOR EMBOLISM

Tumor embolism is rare. Reports of 3 cases have been found in the literature, and there was 1 case in the present series. In 2 of the cases reported [f] a patient with carcinoma of the stomach died of congestive heart failure for no apparent reason. At autopsy the only change observed in the heart was slight hypertrophy of the right ventricle. Microscopically many of the small pulmonary arteries were thrombosed. In some arteries the thrombus was completely organized and showed no tumor; in others the thrombus was more recent and contained more or less degenerate carcinoma cells, and in still others well preserved tumor cells lay free in the lumen. The presence of tumor cells in the lumen causes thrombosis, and ultimately the tumor cells die. The heart failure in these cases was attributed to the obstruction to the pulmonary arteries caused in this way. In 1 case [271] the only tumor that was present in the lungs was within the vessels. In the other cases there was also a

(*e*) 99, 140.
(*f*) 151, 271.

great deal of tumor in the peribronchial and perivascular lymphatic vessels. In the third case [327] the patient died of carcinoma of the pancreas. At autopsy masses of carcinoma cells embedded in thrombus were present in the endocardium of the tricuspid valve and the right ventricle and in some of the small pulmonary arteries. As the thrombus organized, the tumor cells died.

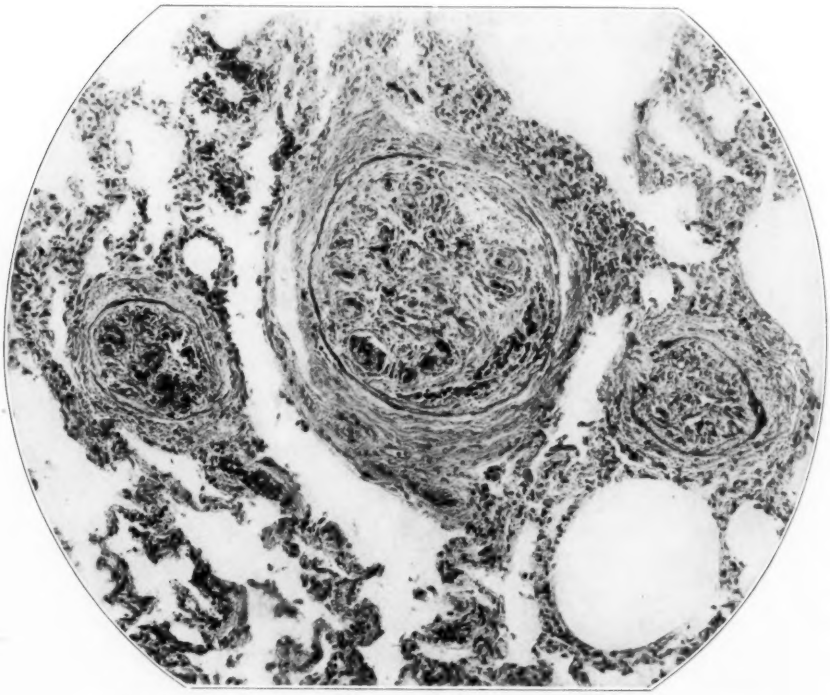

Fig. 33.—Photomicrograph of a section of a tumor embolism of the pulmonary arteries (×115; stained with methylene blue and eosin). Three small pulmonary arteries filled with organized recanalized thrombus and containing clumps of carcinoma cells are shown.

The patient in the present series was a man of 64 with extensive abdominal carcinomatosis. The primary growth was not found. At autopsy no secondary deposits were seen in the lungs. The heart was slightly enlarged as a result of hypertrophy of the left but not of the right ventricle. Coronary arteriosclerosis was observed.

Microscopically (fig. 33) several small pulmonary arteries in both lungs showed tumor emboli. The growth was confined to the lumen of these vessels. There was none in the pulmonary parenchyma. In some vessels the carcinoma cells lay

loose in the lumen, but even in these the intima showed marked thickening by lamellar connective tissue. In most cases the lumen was blocked by an organized and canalized thrombus containing clumps of more or less degenerate tumor cells. In a few cases the organization was of longer standing, the connective tissue being dense and hyaline, and no tumor cells were visible. In one artery there was an outer layer of the intima consisting of dense hyaline connective tissue without tumor cells and a thicker, more cellular, inner layer of organized thrombus containing degenerate tumor cells, while the lumen contained loose well preserved tumor cells. In this artery there was thus evidence of three superimposed tumor embolisms of different ages. Some of the arterioles near the affected arteries, obviously branches of them, showed similar changes.

It is probable that tumor embolism of the pulmonary vessels is commoner than is usually supposed but is missed in the absence of thorough microscopic examination, as there are no gross changes. The tumor cells may enter the veins of the primary growth directly or they may travel along lymphatic vessels to enter the veins through the thoracic duct and so be carried to the lungs. Probably usually, as in the cases here reported, the involvement of the pulmonary vessels is of no great consequence, but occasionally [f] it may be so extensive as to embarrass the heart and even cause death from heart failure.

INVASION FROM WITHOUT

Invasion from without is much commoner and occurred in 7 cases in the present series. The commonest site was the perivascular lymphatic vessels, which sometimes were widely involved and thus much more conspicuous than in health. In 2 cases the deposits were confined to this site, but in 5 cases the other coats of some vessels were involved.

Large Arteries.—Apart from deposits in the perivascular lymphatic vessels, the large arteries were involved in only 1 case, that of a man of 25 with multiple myelomas and a large mediastinal mass invading the lungs. In that case an artery 8.4 mm. in diameter showed extensive infiltration of all the coats by tumor, which separated and in places destroyed the elastic laminae of the media and formed large masses in the intima. In many other arteries the perivascular lymphatic vessels were full of tumor growth.

Small Arteries.—These were involved in the foregoing case and in a case of sarcoma of the leg with secondary mediastinal deposits invading the lung. In both cases many small arteries showed deposits in the adventitia. Many showed endarteritis, the intima being greatly thickened by loose connective tissue containing many lymphocytes and large mononuclears and a few polymorphonuclears. A few capillary lumens also were present. Most of these vessels showed many tumor cells among the round cells. These usually seemed to penetrate to the intima through the media, which was also infiltrated, but sometimes the tumor grew

along the intima for long distances, forming a column of growth hollowed out for the passage of blood. Such an artery, if cut transversely, sometimes showed growth in the intima and little or none in the media and adventitia, though almost certainly the growth originally grew into the intima through the media.

Arterioles and Venules.—These were affected in the case of multiple myeloma. In many instances the walls were greatly thickened and consisted of delicate fibrillar connective tissue infiltrated with growth. The lumen was often greatly narrowed.

Capillaries.—These were also involved in this case. The tumor invaded the alveolar walls, and many alveolar capillaries were blocked by the growth.

Small Veins.—These were involved in 4 cases: the cases of multiple myeloma and secondary sarcoma just mentioned, a case of carcinoma of the stomach in a man of 50 and a case of Hodgkin's disease in a man of 72. Tumor was commonly present in the adventitia, and the walls were infiltrated from without, often with an accompanying endophlebitis similar to the inflammatory reaction in the small arteries. The greatly thickened wall of the vein consisted of delicate fibrillar connective tissue with many lymphocytes, large mononuclears and capillary lumens as well as tumor cells. The lumen was often considerably narrowed and in the case of sarcoma was often completely obliterated by necrotic tumor tissue. In some cases the necrotic tumor showed beginning organization with the ingrowth of new capillaries and fibroblasts. In the case of myeloma the tumor often grew for long distances along the intima, and there was great narrowing of the lumen, while little or no tumor was present in the media or adventitia. Possibly there the tumor had reached the veins by extension from the blocked capillaries in the alveolar walls. Fried [107] also mentioned the tendency for a tumor to grow along the veins. Perhaps the common involvement of the veins accounts for the frequency of cerebral metastases in cases of intrathoracic neoplasm.

Large Veins.—These were involved in only 1 case. There were metastases from a carcinoma of the pancreas in the perivascular lymphatic vessels, and they had just begun to invade the media.

COMMENT

With regard to the influence of neoplasm on the occurrence of pulmonary arteriosclerosis, Jores [138] said that in patients with carcinomatous deposits in the perivascular lymphatic vessels thrombosis of the small pulmonary vessels may occur. This opinion was based chiefly on a case described by Rössle.[252] In the present series 2 patients with

perivascular deposits showed marked sclerosis of the affected vessels, and in 2 others organized thrombi were present. But these changes were so common in the absence of tumor that no conclusions can be drawn. There is no doubt, however, as to the association with endarteritis and endophlebitis in the cases of myeloma and sarcoma, in which the intima of the small arteries and veins that were invaded by growth showed great thickening, with the presence of new capillaries, lymphocytes large mononuclears and sometimes polymorphonuclears.

Thus, on the whole, invasion of the pulmonary vessels by tumor is usually of no clinical importance, though invasion of the veins may be associated with the development of cerebral metastases. Occasionally extensive tumor embolism of small arteries or large primary myomas of the walls of the large vessels may obstruct the circulation. The pressure of mediastinal tumors on the pulmonary vessels has also been described as an occasional cause of failure of the right side of the heart.[g]

THROMBOSIS OF THE PULMONARY VESSELS

INCIDENCE

Many individual cases have been described, but there have been few systematic studies of thrombosis of the pulmonary vessels. The most important paper was Møller's.[207] He said that Lubarsch in 1,932 autopsies noted 347 cases of pulmonary embolism (18 per cent) and 16 of pulmonary thrombosis (0.9 per cent). On careful examination of the lungs in 176 autopsies Møller noted thrombi in 51 cases (29 per cent), and in these 51 cases 84 thrombi were present. Billings [32] observed 11 thrombi in 1,700 autopsies (0.7 per cent). In the cases described in the literature the large intrapulmonary arteries were chiefly involved. In the present series of 100 consecutive unselected autopsies in which the pulmonary vessels were thoroughly investigated, thrombi were observed in 28 cases, which compares well with the 29 per cent reported by Møller. It is clear that thrombi are commonly present at autopsy but that only careful search will reveal them in many cases. This accounts for the widely different estimates of their frequency given by various authors.

THROMBI IN THE STEM OF THE PULMONARY ARTERY

The only case of thrombus in the stem of the pulmonary artery in the present series was that of a man of 72 who died of pulmonary embolism. A recent nonadherent thrombus spread back from the embolus to the stem of the pulmonary artery, but this was obviously agonal.

(*g*) 163, 164, 182.

Records of 26 cases have been found in the literature.[h] In 6 of these[i] the stem of the pulmonary artery was said to be completely blocked by an old partly organized thrombus. Hart [130] and others suggested that when the stem of the pulmonary artery is gradually blocked by a slowly forming thrombus the circulation through the lungs may be maintained by the widening of the collateral anastomotic channels between the pulmonary and the bronchial vessels. But it is clear that normally complete blockage of the stem of the pulmonary artery must bring the circulation to an end, no matter how slowly the thrombosis develops or how extensive the collateral circulation through the bronchial vessels may be, since the bloood which enters the right heart through the systemic veins will be unable to leave it. The only circumstance in which this need not occur is when there is a patent interauricular or interventricular septum. The blood which enters the right side of the heart may then pass directly to the left side and be carried to the lungs through the dilated bronchial arteries and their anastomoses with the pulmonary capillaries. The patient may be able to live, but he will be profoundly cyanosed, owing to the admixture of venous with arterial blood. But abnormal communications between the two sides of the heart were mentioned in only 2 cases,[j] in both of which a widely patent foramen ovale was present. In 1 case [179] the foramen ovale was found at autopsy to be occluded by a thrombus of recent development, and the patient's sudden death was attributed to this. In the cases in which no abnormal communication was present either the complete occlusion of the artery was due to sudden thrombosis immediately before death in addition to an old parietal thrombus, or during life the thrombus actually did not completely occlude the pulmonary artery, but after death the wall of the artery contracted down so as to come in contact with it. A small lumen is all that is necessary to maintain life. In acute experiments on dogs it has been noted that the systemic blood pressure is not reduced until the cross-sectional area of the stem of the pulmonary artery has been reduced by from 61 to 86 per cent, and death does not occur until the area has been reduced by from 84 to 96 per cent.[112] Probably in cases of gradually developing thrombosis the cross-sectional area of the lumen may be reduced even more without causing death, so that a scarcely perceptible chink may suffice to maintain life. Even in the cases in which the foramen ovale was patent it is doubtful if the occlusion of the pulmonary artery was complete, since cyanosis was only slight.

(*h*) 33, 35, 75, 110, 117, 118, 130, 139, 175, 179, 186, 201, 208, 238, 259, 269, 273, 285, 292, 309.

(*i*) 35, 75 (case 2), 130 (2 cases), 269, 309.

(*j*) 179, 309.

In all cases the thrombus was old, adherent and often laminated and partly organized. The heart at autopsy sometimes showed various acquired or congenital lesions, such as mitral stenosis and patent ductus arteriosus, with the changes in the size of the cavities usually associated with these lesions. In most but not all of the patients with no such lesions there was some cardiac enlargement, often especially of the right side. The lungs usually showed merely congestion and edema, though sometimes one or more infarcts were present.

Symptoms.—Symptoms had been present for from one month to several years, but it was difficult to distinguish the symptoms due to the pulmonary thrombus from those of the underlying disease of the heart (which was usually present) and other conditions. In cases of embolism of large pulmonary arteries the heart was usually found to be laboring with a rapid regular rate and accentuation of the pulmonary second sound.[323] In some cases there were to-and-fro murmurs over the pulmonary artery, perhaps due to dilatation of the fibrous ring about the pulmonary valve or to close approximation of the engorged vessel to the wall of the chest. Signs of failure of the right side of the heart were sometimes present. The electrocardiogram in some cases showed a prominent Q and an inverted T wave with a somewhat high origin in lead III, suggesting occlusion of the coronary artery. The clinical features sometimes also closely resembled those of occlusion of the coronary artery.[18] In most of the reported cases of thrombosis of the stem of the pulmonary artery, however, there was no sudden onset of symptoms to suggest embolism. Dyspnea on exertion was always present but was sometimes slight. Cyanosis was usually present but sometimes was absent.[k] The heart was usually enlarged even in the absence of independent cardiac disease, but sometimes there was no clinical enlargement.[l] Occasionally the thrombosed pulmonary artery threw a particularly dense shadow on the roentgenogram.[309]

Most patients died of gradually progressive heart failure. In 2 cases death was sudden: in 1 case [231f] there was hemoptysis, attributed to the closure of the patent foramen ovale by a thrombus; in the other [285] there was an attack of cardiac pain. In 2 cases death was due to intercurrent disease (pneumococcic meningitis [33] and pyelonephritis secondary to tabes dorsalis [130]).

It is thus clear that the condition can rarely be diagnosed during life. The onset is gradual, and the symptoms are those of ordinary congestive heart failure, which might well be due to the underlying cardiac disease, which is usually present. Sometimes the symptoms are so slight that the patient dies of intercurrent disease and there is little to draw attention to the cardiovascular system.

(*k*) 35, 118, 130.

(*l*) 139, 238.

THROMBOSIS OF THE MAIN RIGHT AND LEFT PULMONARY ARTERIES

In 3 cases in the present series thrombosis was present in the main right and left pulmonary arteries. In all the cases the thrombi were recent and unorganized.

The first patient, a man of 51, died in ten minutes of pulmonary embolism seventeen days after cholecystectomy. The right and left pulmonary arteries and the artery to the lower lobe of the right lung contained slightly adherent unorganized thrombi, undoubtedly embolic.

The second patient was a woman of 52 with a blood pressure of 176 systolic and 90 diastolic, syphilitic aortitis and a slightly enlarged heart. She died in a few hours with pain in the right side of the chest, tachycardia and râles at the base of the right lung sixteen days after an operation for mastitis. The right pulmonary artery was occluded by a thrombus which was slightly adherent to the posterior wall. This extended, gradually tapering, for about 6 cm. into the branch to the lower lobe of the right lung. There was a separate and apparently older thrombus in the branch to the upper lobe. Several small thrombi in smaller branches were present in the upper lobe of each lung. All were unorganized, but there was chronic or subacute periarteritis, older than that in the thrombi, in many of the thrombosed vessels. The thrombi were probably embolic but possibly may have been secondary to the periarteritis and were formed in situ.

The third patient, a man of 72, sixteen days after amputation of the left leg for gangrene, suddenly became cyanosed from the level of the nipples upward. Respiration was slow and labored, and there was marked bulging of the veins of the neck and face. He died in a few minutes. There was a large thrombus in the left iliac vein and a large unorganized clot extended from the right ventricle to the stem of the pulmonary artery and its right and left branches. This was undoubtedly an embolus with superimposed thrombosis.

Many cases of thrombosis of the main artery to one or both lungs have been reported.[m] The main artery to one or the other lung was thrombosed in 11 (6 per cent) of Møller's 176 consecutive cases at autopsy. Often one artery was completely blocked.[n] In a few cases both pulmonary arteries were completely occluded.[o] This is no more compatible with the continuance of the circulation than is occlusion of the stem of the pulmonary artery unless there is an abnormal communication between the two sides of the heart or a patent ductus arteriosus. Here, too, it is probable that the occlusion was completed by a terminal acute thrombosis superimposed on a chronic thrombosis immediately before death or that a small lumen, which escaped detection, actually was present. In many cases the thrombus in one or both arteries was parietal, allowing an appreciably free lumen. In most cases the thrombi were old, laminated and partly organized. In 1 case [141] the

(*m*) 24, 32, 33, 39, 75, 76, 98, 117, 118, 130, 131, 139, 141, 170, 175, 177, 179, 183, 186, 200, 201, 207, 208, 231, 235, 238, 260, 262, 263, 269, 282, 285, 292, 309, 311.

(*n*) 39, 75, 130, 141, 199, 231, 235, 292.

(*o*) 75, 179, 309.

organization was complete, and the left pulmonary artery from its origin to the hilus of the lung consisted of a cord of dense fibrous tissue containing many capillary lumens.

Symptoms.—In most cases there were no symptoms pointing to the sudden occlusion of a large pulmonary artery, though in some cases [p] the patient, who had been ill for weeks previously, died suddenly or within a few hours, with pain in the chest, dyspnea and cyanosis. In those cases the thrombus was old and partly organized. Probably, therefore, the terminal symptoms were due to sudden thrombosis superimposed on an old thrombus with sudden completion of the occlusion of the lumen. In a few cases, in patients previously well or suffering from diseases not connected with the cardiovascular system progressive and ultimately fatal heart failure was initiated by the sudden onset of symptoms, such as dyspnea, cyanosis, hemoptysis and pain in the chest, and in some of those the patient also died suddenly. In those cases no doubt the onset of symptoms was due to thrombosis or embolism of a pulmonary artery, and the sudden death was due to the completion of the occlusion or to occlusion of the other artery.[q] In other cases [76] heart failure had previously been present but suddenly became worse. It is difficult to say whether or not the initial heart failure was due to pulmonary thrombosis, but no doubt the thrombosis caused the final accentuation of the symptoms.

In all the other cases there were no symptoms pointing to pulmonary thrombosis, and occasionally [r] there were no circulatory symptoms at all, the patients dying of intercurrent disease. In most cases the first symptoms were those of gradually increasing heart failure, though occasionally repeated hemoptysis [s] or pyrexia was the first symptom. Dyspnea was nearly always, and cyanosis usually, present at some stage. The lungs usually showed only the physical signs of passive congestion or of independent pulmonary disease, but occasionally there were areas of feeble breath sounds, an impaired percussion note and pleural friction over areas where infarcts were later found. The heart was usually a little enlarged and sometimes showed the signs of independent cardiac disease. Occasionally the pulmonary second sound was accentuated or even followed by the diastolic murmur of pulmonary incompetence,[183] but usually the pulmonary second sound was not remarkable or was even weaker than usual.[200] Occasionally there was a loud systolic murmur transmitted to the lung supplied by the thrombosed artery.[141] Roentgenograms often showed special prominence of the

(*p*) 39, 235, 260.
(*q*) 32, 75, 183, 262.
(*r*) 33, 131.
(*s*) 98, 311.

pulmonary artery and sometimes dense shadows corresponding to the thrombosed vessel.[t] The electrocardiogram usually showed no abnormality or else changes associated with independent cardiac disease, but occasionally there was right axis deviation.[u] Death was almost always due to gradually progressive congestive heart failure, though occasionally it was sudden.

Postmortem Observations.—At autopsy the heart occasionally appeared normal.[v] Often there was independent rheumatic, syphilitic or congenital cardiac disease. Occasionally there was marked hypertrophy of the right ventricle for which no cause other than the thrombosis could be found.[w] In other cases the right ventricle was of normal thickness. This was especially noteworthy in Karsner's case of complete obliteration of the left pulmonary artery by an organized thrombus,[141] in which the absence of hypertrophy of the right ventricle, in spite of complete occlusion of the left pulmonary artery of long standing, was striking. In spite of the occlusion of the artery the lungs always showed congestion and rarely infarction.

Thus, in cases of thrombosis or chronic embolism of the main artery to one lung distinctive symptoms were unusual. In most instances the patient showed gradually progressive heart failure without a sudden onset, and the symptoms usually appeared either in the course of preexisting heart failure or in patients in whom independent cardiac disease in itself made them liable to heart failure. Therefore, thrombosis can rarely be diagnosed.

THROMBOSIS OF THE LARGE INTRAPULMONARY BRANCHES

Thrombosis of the large intrapulmonary branches of the pulmonary artery occurred in 13 cases in the present series. In 10 the thrombi were seen macroscopically, and in 3 they were discovered microscopically. The cases were as follows:

CASE 1.—A woman of 78, who had had both feet amputated because of gangrene seven years before, was cyanosed and dyspneic. There was edema of the legs and ascites. The blood pressure was 180 systolic and 100 diastolic. The heart was enlarged. At autopsy the portal vein was thrombosed. There was hypertrophy of the left but not of the right ventricle. The lungs were congested and edematous without infarcts. No thrombosed arteries were seen grossly, but microscopically an artery 2.5 mm. in diameter in the right lung was observed to be blocked by a thrombus composed of fused platelets, red cells, white cells and fibrin and to show many areas of early organization, as indicated by the ingrowth of new capillaries and fibroblasts. It is doubtful whether the thrombus was embolic or had formed in situ.

(*t*) 39, 309.
(*u*) 24, 139.
(*v*) 75, 263.
(*w*) 24, 139, 292.

CASE 2.—A child aged 13 months died of generalized tuberculosis. There was a large cavity in the upper lobe of the right lung. An artery near this was converted into a fibrous cord. Microscopically a completely organized thrombus was seen. In this case the thrombus was no doubt the result of the presence of a cavity in the immediate neighborhood.

CASE 3.—A man of 73 had emphysema. After removal of a vesical tumor bronchopneumonia developed and he died. The heart weighed 450 Gm. and the right ventricle was slightly thickened (5 mm.). There were thrombi in the perivesical veins. A firm, pale, adherent thrombus occluded the branch of the pulmonary artery to the lower lobe of the left lung for 2 cm. beyond its origin. Beyond that it was capped by a recent nonadherent clot. Old thrombi extended into some of the primary branches of the artery. Similar old thrombi were present in arteries about 5 mm. in diameter in the upper lobe of the left lung and the middle and lower lobes of the right lung. Microscopically the thrombi were seen to be organized at their base, with the ingrowth of new capillaries and fibroblasts. There were masses of large pigment-filled cells at the periphery. Evidently there had been an embolism from the pelvic veins with secondary superimposed thrombosis. Organization was well advanced, showing that the clots had been in situ for several days. Though the blood supply of the whole lower lobe was cut off, there were no symptoms of embolism and no infarcts.

CASE 4.—A woman of 87 with chronic fibroid pulmonary tuberculosis and emphysema had progressive dyspnea and edema for one and one-half years. The right ventricle was slightly thickened (5 mm.). There was a thrombus in the inferior vena cava. The artery to the lower lobe of the right lung was occluded for about 5 cm. by a firm, white, adherent thrombus, organized at its base and extending into the main branches. The lumen of an artery 5 mm. in diameter in the lower lobe was almost occluded by a thrombus of red blood cells and fibrin. The surface of the thrombus was covered by proliferated endothelium, and there was an early ingrowth of fibroblasts and new capillaries. Here, too, there was probably embolism with secondary thrombosis. There were no symptoms of embolism and no infarcts.

CASE 5.—A man of 51 suddenly became dyspneic and cyanosed and died in ten minutes sixteen days after cholecystectomy. Nonadherent clots were present in the right and left main pulmonary arteries, and a parietal thrombus, also unorganized, was present in the artery to the lower lobe of the right lung. The clots were undoubtedly embolic.

CASE 6.—A man of 50 died of carcinoma of the stomach with deposits in the lungs and bronchial glands. No obvious source of embolism was seen at autopsy. The heart was normal; the right ventricle was of normal thickness. Branches about 5 mm. in diameter in the lower and upper lobes of the left lung were almost occluded by a firm, adherent thrombus, and a larger artery in the lower lobe of the right lung showed a parietal thrombus from 3 to 4 mm. thick. Microscopically the thrombi were laminated and showed early organization. There was ingrowth of connective tissue containing new capillaries, fibroblasts and pigment-containing mononuclears. Several arteries 3 or 4 mm. in diameter in the left lung were greatly narrowed by thrombi, some with early and some with advanced organization. Some of the thrombi that showed advanced organization were attached to the wall of the vessel by a stalk of dense fibrous tissue containing fine elastic fibers in its long axis. In this case the thrombi were perhaps formed in situ.

Case 7.—A woman of 48 died of mediastinal abscess. A pulmonary artery 1.3 mm. in diameter showed extensive leukocytic infiltration of its walls, and its lumen was blocked by a septic embolus consisting of fibrin with many pus cells.

Case 8.—A man of 43 died of syphilitic aortic incompetence and syphilis of the right pulmonary artery (previously described). The artery to the middle lobe of the right lung was blocked by an old adherent but unorganized thrombus. An artery 2.5 mm. in diameter showed at the origin of a large branch, which was almost occluded by an organized thrombus, a horn-shaped mass of fibrous tissue projecting for 1.4 mm. into the lumen. It had a core of dense pink-staining connective tissue and a superficial layer of less dense yellowish-staining connective tissue, with a sheaf of elastic fibers in the boundary zone. Both layers contained capillary lumens, many lymphocytes and large mononuclears and sheets of smooth muscle cells. This seemed to represent a completely organized thrombus projecting into the lumen from the mouth of a thrombosed branch. The presence of elastic tissue and smooth muscle was noteworthy. There was no obvious source of embolism, and the thrombi were perhaps formed in situ.

Case 9.—A man of 69 had aortic stenosis and angina pectoris for eighteen years and congestive heart failure for three months. The heart weighed 700 Gm. The right ventricle was greatly thickened (12 mm.). A small, flat adherent thrombus was present in a large artery in the lower lobe of the left lung. The lumen of an artery 4.8 mm. in diameter was partly blocked by an organized thrombus (figs. 34 and 35). There were many recanalizing lumens, including five large ones (diameter, from 0.415 to 0.598 mm.). Each of these was surrounded by a thick elastic lamina inside which there was patchy intimal thickening up to a maximum of 0.18 mm. by loose connective tissue with many round, spindle and foam cells. There was thus atherosclerosis of the canalizing vessels. Between the lumens were broad sheets of smooth muscle, tending to surround them and form an irregular and incomplete media but also extending to other parts of the thrombus. Between the sheets of muscle cells there were loose fibrillar connective tissue and a little fine elastic tissue. The organized mass was papillary, and several papillae were cut so that they lay loose in the lumen. A part of the intima of the artery away from the thrombus was normal, but the rest was thickened and similar in structure to the organized thrombus It probably represented an original parietal thrombus. In this case, too, the great development of elastic tissue and smooth muscle in the organized thrombus was noteworthy. There was no obvious source of embolism, but the normality of the intima away from the organized thrombus suggested that the thrombus may have been embolic in origin.

Case 10.—A man of 56 died three weeks after suprapubic cystotomy. The lungs were emphysematous. The heart weighed 450 Gm., but the right ventricle was not thickened. There were recent nonadherent thrombi in vessels in both lungs. An artery 3.9 mm. in diameter contained a septic embolus, and its walls were invaded by leukocytes.

Case 11.—A woman of 52 with a slightly enlarged heart and a blood pressure of 176 systolic and 90 diastolic had pain in the chest, tachycardia and râles in the right side of the chest and died in a few hours after the onset of these symptoms, sixteen days after an operation for mastitis. The heart weighed 400 Gm., and the wall of the right ventricle was 5 mm. thick. The right main pulmonary artery was occluded by a recent thrombus, extending for about 6 cm. into the branch to the lower lobe of the right lung. Several branches in the upper lobe of the right lung and one in the upper lobe of the left lung also were blocked by an unorganized thrombus. Many of the thrombosed arteries showed a

subacute or chronic periarteritis, obviously older than the thrombi. The clots were probably embolic, originating in the operative site, but possibly they were secondary to the periarteritis and formed in situ.

CASE 12.—A man of 72, sixteen days after amputation of the left leg for gangrene, suddenly became cyanosed, with dyspnea and bulging of the veins of the neck, and died in a few minutes. There was marked emphysema. The heart weighed 350 Gm., but the right ventricle was not thickened. There was a thrombus in the left iliac vein, and another extending from the right ventricle to the stem of the pulmonary artery, its right and left branches and their primary branches.

Fig. 34.—Photomicrograph of a section of a large pulmonary artery showing an organized thrombus (× 20; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). An organized thrombus is partly occluding the lumen. There are five large and many small recanalizing lumens. Each of the large ones is surrounded by an elastic lamina, inside which is an incomplete irregular layer of connective tissue. Between the lumens are sheets of smooth muscle set in loose connective tissue. The intima of the part of the artery not occupied by thrombus is normal above; below it is thickened by tissue similar in structure to that of the organized thrombus.

This was recent and unorganized. No doubt it represented an embolus with secondary thrombosis.

CASE 13.—A woman of 53 with ascites due to peritoneal metastases from an ovarian tumor died suddenly. There was no obvious source of embolism, though

an ovarian tumor had been removed twelve months previously, and embolism might have occurred after that. The heart was normal. An artery 3 mm. in diameter was almost occluded by a thrombus of platelets and fibrin, with an extensive ingrowth of capillaries and fibroblasts at its base and with its surface covered by proliferated intimal endothelium. The intima over about half the circumference was thickened by dense fibrous tissue containing a few capillary lumens, obviously representing an old organized parietal thrombus, perhaps due to embolism at the time of operation twelve months before. It may be that the recent thrombus was on the basis of the old lesion.

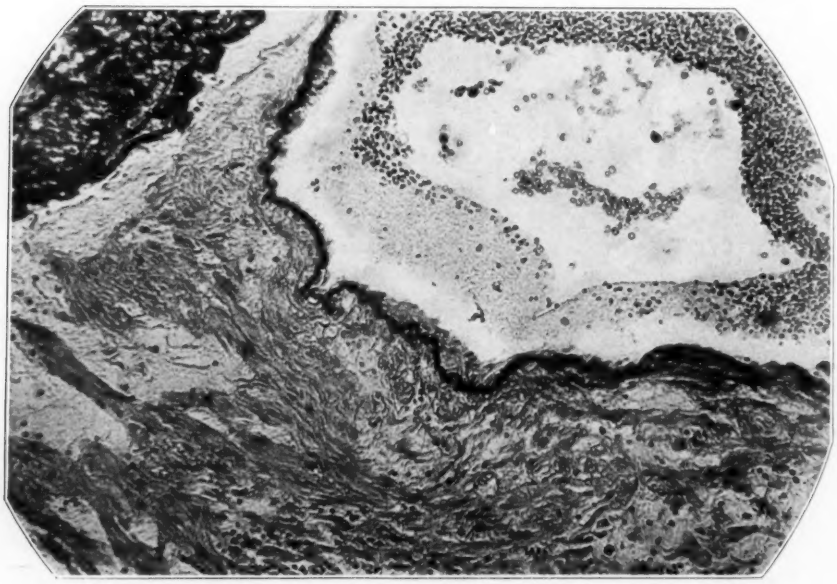

Fig. 35.—Enlargement of a portion of the artery shown in figure 34 (× 157; same stain). In the upper left corner is a small part of the arterial media. The upper right portion of the figure shows a part of one of the canalizing lumens surrounded by an elastic lamina, inside of which there is slight, patchy thickening of the connective tissue. In the lower portion are irregular sheets of smooth muscle cells in the organized thrombus set in loose fibrillar connective tissue.

Summary.—Thus, thrombi were observed in the large intrapulmonary arteries in 13 of 100 consecutive autopsies. In 7 they were almost certainly embolic in origin, though often with superimposed secondary thrombosis. These were present either in patients dying of pyemia or in patients dying a few days after an operation. In 3 instances the patients died suddenly with symptoms of pulmonary embolism. In only 4 were there circulatory symptoms apart from those of pulmonary

embolism, and in each of these independent cardiac disease, capable in itself of causing the symptoms, was present. In 5 cases the thrombi were unorganized. The rest showed varying degrees of organization, with the presence of smooth muscle and elastic tissue in the most advanced cases.

Many cases of thrombosis of the large intrapulmonary arteries have been reported. Sometimes the thrombosis was widespread, involving all the arteries to one lobe [x] or all the arteries of moderate size in both lungs.[177] The thrombi usually occluded the affected arteries, but sometimes they were parietal and they were then often situated on the spur at the bifurcation of an artery.[207] Organization of parietal thrombi sometimes gave rise to bands stretching across the artery, attached to the vessel wall only by their ends or by one edge. Sometimes there were many such bands forming a network across the mouth of one or more branches.[y]

Symptoms.—The symptoms in the cases reported were varied. Evidence of venous thrombosis was present in more than half the patients with large thrombi and in less than a third of those with small thrombi.[207] Occasionally there was a sudden onset of symptoms, including dyspnea, cyanosis, hemoptysis or pain in the chest, followed by gradually progressive heart failure.[z] But in most cases the symptoms were merely those of gradually increasing heart failure, which might well have been due to the underlying cardiac disease. Cyanosis was sometimes marked but was often slight or absent.[a] Symptoms pointing to sudden occlusion of the pulmonary arteries were, as in the present series, more often absent than present. Møller [207] said that symptoms such as sudden dyspnea, fainting, feeble pulse, pallor, pain in the chest and bloody expectoration were present in 22 of 23 patients with large thrombi which were directly fatal and in 21 of 42 patients with small thrombi not in themselves fatal. When there were small thrombi only one or two of these symptoms were present, and diagnosis was difficult. In 1 of Brenner's cases [43] the patient, who had been slightly dyspneic for several months, suddenly became more dyspneic on the morning of his death. During the day he had four syncopal attacks accompanied with pallor and feeble pulse and died during the fourth attack. Four large arteries were occluded by thrombus, and no doubt each attack corresponded with the occlusion of one of these. In several other cases patients who had previously shown signs of heart failure died suddenly or rapidly with symptoms of heart failure.[b]

(*x*) 186, 192.
(*y*) 207, 265.
(*z*) 32, 75, 98, 262.
(*a*) 32, 43, 192, 262.
(*b*) 32, 76, 183, 262.

Physical signs of independent pulmonary disease were commonly present. Occasionally there were signs due to infarcts (impaired percussion note, feeble bronchial breathing and pleural friction).[c] Signs of independent cardiac disease were commonly present. In a few cases the heart was slightly enlarged. Occasionally there was marked accentuation of the pulmonary second sound,[d] and in 1 [183] there was a diastolic murmur of functional pulmonary incompetence. Occasionally the heart was apparently normal.[e] Roentgenograms rarely helped in making a diagnosis, though occasionally a shadow representing a pulmonary infarct was present.[f] The electrocardiograms never gave any help.

Course.—Death was almost always due to progressive heart failure. Occasionally it was sudden;[g] occasionally it was due to intercurrent disease.[h] The prominence of circulatory symptoms in the cases reported was no doubt due to the fact that in their absence the pulmonary arteries are rarely examined. In the present series in many cases there were no circulatory symptoms and the thrombi were discovered only on routine examination of the arteries. Probably the majority of thrombi in large intrapulmonary arteries cause no symptoms. At autopsy there was occasionally slight enlargement of the right side of the heart in the absence of independent cardiac disease. The lungs usually showed only congestion and edema, but sometimes there were infarcts.

THROMBOSIS OF THE SMALL MUSCULAR ARTERIES

Thrombosis of the small muscular arteries occurred in 19 cases in the present series. It is comparatively rarely mentioned in the literature, because it can be observed only with the microscope.

CASE 1.—A man of 68 had emphysema and a slightly enlarged heart. After suprapubic cystotomy pyrexia and auricular fibrillation developed, and he died in two weeks. At autopsy there was a suppurating periprostatitis. There were septic infarcts in the lungs. The heart weighed 375 Gm., and the right ventricle was not thickened. Most of the small pulmonary arteries showed marked intimal thickening with narrowing of the lumen. Some were partly or completely blocked by thrombi in varying stages of organization, some consisting of red blood cells, leukocytes and fibrin, covered by proliferated endothelium and showing ingrowth of capillaries and fibroblasts at the base. In others the whole thrombus had been converted into a mass of connective tissue containing capillary lumens and many polymorphonuclears and large mononuclears, some full of blood pigment. Some of these, obviously representing organized parietal thrombi, projected into

(*c*) 32, 76, 139, 175, 192.
(*d*) 98, 183.
(*e*) 43, 139.
(*f*) 43, 139, 176.
(*g*) 43, 75, 179, 262, 285.
(*h*) 43, 74.

the lumen as horn-shaped masses of vascular cellular connective tissue. The recent thrombi were probably embolic, secondary to the periprostatic suppuration. Possibly the older ones also were embolic, but they obviously dated from before the operation.

CASE 2.—A woman of 38 had pyemia after radium treatment for carcinoma of the uterus. There were an abscess of the broad ligament, thrombosis of the pelvic veins and septic pulmonary infarcts. Some of the small muscular arteries were blocked by recent emboli of fibrin and leukocytes.

CASE 3.—A woman of 68 died of pulmonary tuberculosis. The right ventricle was not thickened. In an artery 0.5 mm. in diameter a truncated cone of fibrous tissue, representing an organized parietal thrombus, projected for 0.16 mm. into the lumen over a base of 0.5 mm. Beneath it the elastica interna frayed out and disappeared, and the underlying media was replaced by dense connective tissue. There was no obvious source of embolism, and perhaps the thrombus was formed in situ.

CASE 4.—A woman, whose case was recorded previously as case 1 of thrombosis of the large elastic arteries, died at the age of 78. Many small arteries, from 0.16 to 0.75 mm. in diameter, were partly or completely blocked by dense connective tissue containing capillary lumens and sometimes showing a great deal of irregular elastic tissue. These represented old organized thrombi, possibly embolic in origin, which probably came from the gangrenous extremities seven years before.

CASE 5.—A woman of 67 died of cerebral thrombosis the day after one leg was amputated for gangrene. The lungs were emphysematous. The right ventricle was thickened (6 mm.). Two horn-shaped masses of dense connective tissue containing some longitudinal elastic fibrils projected into the lumen of an artery 0.42 mm. in diameter. These evidently were organized parietal thrombi, possibly arising as emboli from the gangrenous leg.

CASE 6.—A boy of 16 died of congestive heart failure. The heart weighed 500 Gm., and the right ventricle was thickened (6 mm.). There was no valvular lesion. There were two infarcts in the lower lobe of the right lung. A mass of dense connective tissue containing capillary lumens projected into and greatly narrowed the lumen of an artery 0.34 mm. in diameter. There was no obvious source of embolism.

CASE 7.—A man of 60, who had the right leg amputated for diabetic gangrene one year before, died of cerebral thrombosis two weeks after amputation of the left leg for gangrene. The right ventricle was normal. Two arteries 0.66 mm. in diameter were blocked by dense connective tissue containing capillary lumens. Evidently these were organized thrombi, possibly arising one year before as emboli from the gangrenous leg.

CASE 8.—A woman of 58 died of agranulocytosis. The heart weighed 500 Gm. The right ventricle was dilated. An artery 0.5 mm. in diameter was blocked by loose connective tissue containing two capillary lumens. Evidently this was an organized thrombus. There was no obvious source of embolism.

CASE 9.—A woman of 52 with a blood pressure of 170 systolic and 95 diastolic died of peritonitis. The heart weighed 425 Gm., and the right ventricle was 6 mm. thick. Two arteries, 0.30 and 0.42 mm. in diameter, were blocked by loose connective tissue containing fine elastic fibers, capillary lumens, red blood cells, lymphocytes, fibroblasts and pigment-containing large mononuclears. Another artery showed great uneven thickening of the intima of similar type, with extreme

narrowing of the lumen, probably due to an organized parietal thrombus. There was no obvious source of old emboli, and perhaps the thrombi were formed in situ.

CASE 10.—A man, whose case was recorded previously as case 6 of thrombosis of the large elastic arteries, died at the age of 50. Several arteries from 0.12 to 0.21 mm. in diameter were blocked by fibrous tissue containing from one to three capillary lumens. Several other arteries of the same size had their lumens almost exactly half occluded by a mass of dense connective tissue with a straight edge. In spite of the absence of capillary lumens, these were probably organized parietal thrombi. In several somewhat larger arteries (with a diameter of from 0.4 to 0.5 mm.) there were more recent thrombi of fibrin, platelets and leukocytes, with organization at the edges. In some of these the intima away from the thrombus was thickened and similar in structure to the organized part of the thrombus. Perhaps this represented organization of an older parietal thrombus.

CASE 11.—A man, whose case was recorded previously as case 8 of thrombosis of the large elastic arteries, died at the age of 43. The lumen of an artery 0.9 mm. in diameter was blocked by connective tissue with several capillary lumens, many round and spindle cells and strands of smooth muscle cells. The lumens of other vessels were blocked by loose cellular connective tissue with one or two capillary lumens. Others showed organized parietal thrombi of similar structure. Many of the thrombosed vessels showed portions of the media replaced by dense connective tissue, with round cells and new vessels. It is doubtful whether this was a syphilitic lesion (there was definite syphilis of the aorta and of a large pulmonary vessel) with superimposed thrombosis or whether it represented the ingrowth of vessels and connective tissue from the adventitia to the thrombus in the process of organization.

CASE 12.—A man with tumor emboli of some of the small pulmonary vessels, whose case was described under the heading tumor of the pulmonary arteries, died at the age of 53.

CASE 13.—A woman of 77 died of pulmonary and intestinal tuberculosis. The heart weighed 200 Gm., and the right ventricle was 2 mm. thick. In the dense apical tuberculous scars the intima of all the small arteries was greatly thickened by dense connective tissue, sometimes with complete obliteration of the lumen except for a few capillary lumens. In one artery a large part of the media was replaced by dense fibrous tissue. The thrombosis was probably a response to the surrounding tuberculous process.

CASE 14.—A man, whose case was recorded as case 9 of thrombosis of the large arteries, died at the age of 66. An artery 0.2 mm. in diameter and one of its branches as well as several surrounding arterioles were blocked by dense fibrous tissue, sometimes with a few capillary lumens. The thrombus appeared to have arisen in the parent artery and spread to the branches. There was no obvious source of embolism.

CASE 15.—A man, whose case was recorded previously as case 10 of thrombosis of the large arteries, died at the age of 56. An artery 0.55 mm. in diameter was almost obliterated by a mass of fibrous tissue with two capillary lumens. Another artery showed a horn-shaped mass of dense fibrous tissue projecting into the lumen. These probably represented organized parietal thrombi. They seemed to have been present for a longer time than the postoperative urinary infection.

CASE 16.—A man of 65 died of carcinoma of the pancreas with no circulatory symptoms. The heart was normal. A mass of dense fibrous tissue with a base

of 0.17 mm. projected for 0.14 mm. into the lumen of an artery 0.18 mm. in diameter. This probably was an organized parietal thrombus. There was no obvious source of embolism.

CASE 17.—A woman of 65 had carcinoma of the stomach and pulmonary tuberculosis but no circulatory symptoms. The heart was normal. A mass of dense fibrous tissue projected for 0.11 mm. on a base of 0.19 mm. into the lumen of an artery 0.25 mm. in diameter. This was probably an organized parietal thrombus. There was no obvious source of embolism.

CASE 18.—A man of 50 died of hematemesis. There were no circulatory symptoms. The heart was normal. A horn-shaped mass of fibrous tissue projected for 0.19 mm. on a base of 0.08 mm. into the lumen of an artery 0.76 mm. in diameter. Another similar mass in the same artery was cut transversely and seemed to lie loose in the lumen. The masses seemed to be organized parietal thrombi. There was no obvious source of embolism.

CASE 19.—A woman of 77 had auricular fibrillation and dyspnea for 5 months. The heart was normal, but syphilitic aortitis was present. An artery 0.27 mm. in diameter showed several masses of fibrous tissue, representing organized parietal thrombi, projecting into the lumen.

Thus, thrombosis of the small pulmonary arteries was commonly observed in the present series. It could be seen only on systematic microscopic examination of the lungs. Usually only a few arteries were involved, and probably if more blocks had been taken from each lung the condition would have appeared even commoner. In 5 cases the thrombi were almost certainly embolic. In the others there was no obvious source of embolism, and the possibility of their having been formed in situ must be considered. Circulatory symptoms were present in only 5 cases, and in all of these there was independent cardiovascular disease which amply accounted for them.

Thrombi in the small vessels were usually more completely organized than in the large vessels, perhaps because they were older. An alternative explanation is that the surface of the thrombus exposed to the ingrowth of new capillaries is relatively larger as compared with the volume of thrombus to be organized.

Thrombosis of the small pulmonary arteries has been reported relatively rarely, probably owing to the lack of systematic microscopic examination of the lungs, but a few isolated cases have been mentioned.[i] Occasionally[j] the thrombosis was so extensive as to cause hypertrophy of the right ventricle and heart failure.

THROMBOSIS OF ARTERIOLES

Thrombosis of arterioles was found in only 3 cases in the present series, and in each case the thrombi seemed to spread from small

(*i*) 20, 37, 61, 98, 107, 109, 117, 157, 179, 226, 300.

(*j*) 117, 151, 271.

arteries of which the arterioles were branches. The cases are recorded as cases 4, 12 and 14 of thrombosis of small arteries. In each the thrombi were similar in structure to those in the parent vessels.

THROMBOSIS OF SMALL VEINS

Thrombosis of small veins occurred in 1 case in the present series.

The patient, a man of 56 with emphysema and acute superimposed on chronic rheumatic carditis, died of congestive heart failure. In one small vein the intima showed three sharply localized thickenings, the largest being 0.18 mm. long and 0.1 mm. thick. The thickenings consisted of loose connective tissue with many fibroblasts, large mononuclears and blood cells and a few elastic fibrils. The thrombosis could not have been embolic. Possibly stasis in the pulmonary veins, perhaps with a local rheumatic lesion of which no trace remained, determined the occurrence.

Thrombosis of pulmonary veins has rarely been reported. Isolated instances have been described in cases of pneumonia,[k] pneumonoconiosis [256] and primary pulmonary venous sclerosis.[98] Some of the thrombi were organized and recanalized. Occasionally the mouths of the pulmonary veins were blocked by a thrombus in the left auricle in cases of mitral stenosis.[l] Apart from that, pulmonary venous thrombosis evidently plays only a small part in the pathologic conditions of the pulmonary circulation.

ETIOLOGY OF PULMONARY THROMBOSIS

In the present series there was an obvious source of embolism in 7 of the 13 cases of thrombosis of the large arteries and in 6 of the 19 cases of thrombosis of the small arteries. Probably the thrombi in these cases were embolic in origin, but that was absolutely certain only in the case of tumor embolism. In the cases in which there was no obvious source of embolism, emboli may have arisen from some unrecognized source, or the thrombi may have formed in situ. When embolism is the primary event, secondary thrombosis before and behind the embolus usually occurs, so that branching of the thrombus along the ramifications of the pulmonary artery does not disprove its embolic origin. Glynn [116] expressed the belief that even thrombi that occur in septic conditions or after operations are really formed in situ. He described 8 such cases of what would ordinarily be called pulmonary embolism. All the patients died suddenly or rapidly. He adduced the following evidence in favor of the conclusion that the thrombi were formed in situ:

(*k*) 37, 248.

(*l*) 184, 273.

A. Macroscopic Appearances.—1. In all but 1 case the thrombus was laminated (but a laminated thrombus in a systemic vein may break off to form an embolus, though softer and more quickly formed coagulation thrombi are more likely to do so;[249] or a thrombus may gradually be deposited on a small pulmonary embolus).

2. In 5 cases there were thrombi in the small branches separate from those in the large (but this may have been due to multiple embolism or to stagnation in the small vessels distal to the obstructed large vessels).

3. It is impossible for laminated thrombi, which often extend into the terminal ramifications, to be deposited during the period of from five to thirty minutes between the onset of symptoms and death (but it is probable that no symptoms would arise from a moderate-sized embolus until enough secondary thrombosis had occurred to block a large part of the pulmonary arterial bed).

B. Microscopic Appearances.—1. In all the patients examined, hemosiderin had spread into the wall of the vessel, a change which requires days to develop. (This proves that the thrombi had been several days in situ, but it does not disprove that they had been carried there from a systemic vein.)

2. Three of the thrombi showed some organization (the same objection holds for this argument).

The opposite standpoint, that pulmonary thrombi are almost always embolic, was taken by Møller.[207] In only 2 of his 51 patients, both with thrombo-arteritis secondary to local inflammation in the lung, were the thrombi undoubtedly formed in situ. Møller said that it is often possible to distinguish microscopically between autochthonous thrombi and old adherent emboli. The former are formed slowly; there are thick, closely set bands of platelets perpendicular to the wall of the vessel, and red blood cells are scanty. Emboli are usually formed by dislodged stagnation thrombi, which are rapidly formed and contain many red blood cells and no well formed bands of platelets. Dislodgment of agglutination thrombi, similar in structure to the autochthonous pulmonary thrombi, is rarer because they are more firmly adherent to the wall of the vein, and when it does occur, the bands of platelets are not perpendicular to the walls of the branch in which the embolus lodges. The presence of a great deal of iron in even a completely organized thrombus shows that it originally contained many red blood cells, so that it was of embolic origin. Using these criteria, he concluded that the great majority of the 84 thrombi in his 51 cases were embolic. Four were fresh stagnation thrombi. In 52 there was partial or complete organization, but there were remnants of fibrin and red blood cells and a great deal of iron pigment. Often iron pigment is observed in the wall of the vessel; so probably it is ultimately all removed. It is then impossible to decide

the origin of the thrombus or even to differentiate it from an arteriosclerotic plaque. Often the amount of secondary thrombosis superimposed on the embolus is much greater than the original embolus; so it can be concluded with certainty that the clot was not embolic only if its whole extent is examined. In the case of 9 organized thrombi it was impossible to conclude whether the clots were embolic.

In the present series a much greater proportion of the clots were organized and contained little or no blood pigment. Moreover, it seems that Møller attached too much importance to the presence of old blood pigment. Some red blood cells are present in the most gradually formed clots, and even when the occlusion of the pulmonary artery is begun by an autochthonous agglutination thrombus, it commonly is completed, when the narrowing has progressed far enough, by a quickly formed stagnation thrombus containing many red blood cells, which when organized would contain a good deal of iron pigment. The frequency of nonoccluding parietal thrombi argues for formation in situ, since it might be expected that an embolus would travel until it reached an artery just small enough to be occluded. Møller, however, said that an embolus is often arrested by the spur at the bifurcation of an artery much larger than itself. He thus did not completely prove his point, though on the whole it is probable that most pulmonary thrombi are embolic. The lungs, as Aschoff pointed out, form a filter in the course of the circulation in which fragments of thrombus, growth, fat and other material [m] are arrested and prevented from entering the systemic arteries.

Nevertheless, many cases of undoubted autochthonous thrombosis have been described, under the following conditions:

1. In aneurysms of the pulmonary artery, congenital or syphilitic.[n] The thrombus is often laminated and partly or completely occludes the aneurysmal sac.

2. In acute pulmonary arteritis due to local disease of the surrounding lung [o] or complicating patency of the ductus arteriosus.[p]

3. In syphilitic arteritis.[q] Syphilitic aortitis, without aneurysm, is rarely associated with thrombosis, but the occurrence of syphilis and thrombosis at the same point in the pulmonary artery indicates that the thrombus is secondary to the arterial lesion.

Thrombosis has also been described in many cases of primary and secondary pulmonary vascular sclerosis. In the systemic circulation

(*m*) 190, 253.

(*n*) 32, 170, 175, 238, 292, 309, 311.

(*o*) 37, 39, 61, 220.

(*p*) 35, 110, 118, 259, 269.

(*q*) 57, 74, 141, 166, 192, 231.

thrombi often form over atheromatous ulcers, and there is no a priori reason why this should not be so in the pulmonary circulation. But atheromatous ulcers are rare in the pulmonary arteries and were not seen in the present series. In the absence of a broken endothelial surface or of sufficient narrowing of the lumen to cause stagnation, it is difficult to see why atheroma should cause thrombosis. Though in many cases no source of embolism was found, yet, since it is impossible to examine every systemic vein at autopsy, such sources may actually have been present. Therefore, while perhaps many of these cases are actually examples of autochthonous thrombosis, it is best to regard this diagnosis as nonproved.

Comment.—It is therefore probable that except in cases of pulmonary aneurysms, acute arteritis or syphilitic arteritis, in which autochthonous thrombosis may occur, most pulmonary thrombi are of embolic origin, though secondary thrombosis occurs before and behind the embolus. Except when a large embolism occurs in a septic condition with thrombophlebitis, or after an operation, and causes a large pulmonary infarct, the diagnosis is difficult, as the symptoms merge into those of congestive heart failure, which is often already present. Even large thrombi, if there is no independent cardiac disease, commonly do not cause any symptoms. If independent cardiac disease is present, it is possible that large thrombi may add somewhat to the load on the heart and so hasten the fatal issue. Small thrombi are common but probably of little importance.

ANEURYSMS OF THE PULMONARY ARTERY

Aneurysms of small pulmonary arteries in the walls of tuberculous cavities are common and are an important cause of copious hemoptysis. They will not be considered further here. Aneurysms of the stem and main branches of the pulmonary artery are rare, and Scott [278] said that only 90 cases have been reported since 1833. No cases were reported at autopsy at St. Bartholomew's Hospital between 1867 and 1912, though there were 350 cases of aneurysm in that period. Saccular aneurysms are exceedingly rare. Fusiform dilatation is commoner, but it is difficult to demarcate it from the simple dilatation so common in cases of pulmonary arteriosclerosis. In the present series there were several cases of marked dilatation of the stem and main branches, but none great enough to be called aneurysmal. In the case of syphilis of the pulmonary arteries, however, several of the smaller elastic and larger muscular arteries showed localized bulging of their walls where the media had been replaced by vascular fibrous tissue. There were no symptoms which could be referred to that. The cases reported in the literature may be classified as follows:

TYPES OF ANEURYSMS

1. *Traumatic.*—There was only 1 case in this group.[104] In that case there was a gunshot wound of the chest followed by pneumonia and later by repeated hemoptyses. There were dulness and bronchial breathing at the base of the right lung. There was a continuous murmur with systolic accentuation over the right lung. Roentgenograms showed a spherical mass at the root of the right lung. The patient died of hemoptysis. At autopsy an aneurysm the size of an orange was present on the right pulmonary artery about 4 cm. beyond the bifurcation.

2. *Mycotic.*—In several cases aneurysm was associated with infection of a congenital lesion (see the next paragraph). In addition, Salzer [263] described the case of a woman of 60 who died of septicemia following pyelonephritis. The right pulmonary artery just before the hilus showed an aneurysm the size of a bean, filled with an adherent clot. The thrombus and the wall of the aneurysm showed a great deal of leukocytic infiltration. Evidently the aneurysm was due to the lodging of a septic embolus.

3. *Congenital.*—Ten cases have been collected from the recent literature. There were 5 cases in males and 5 in females, and the ages ranged from 4 to 49 years. In 4 [r] there was a patent ductus arteriosus; in 1 there was a widely patent foramen ovale,[309] and in another,[33] stenosis of the infundibulum and a patent interventricular septum. In the others[s] the congenital abnormality was thought to lie in the pulmonary artery itself. In no case was the diagnosis made during life. In 1 [101] there were no circulatory symptoms, and the patient died of tuberculosis. In 3 [t] there were only the signs of congenital cardiac disease complicated by infective endarteritis. In the others the signs of congestive heart failure were present, and in 3 [u] instances erroneous diagnoses of mitral stenosis and aortic incompetence were made. In only 1 were there signs of mediastinal pressure.[309] In that case there were bulging of the manubrium sterni and paralysis of the left vocal cord, and the roentgenograms showed a rounded, nonpulsating mass in the region of the aortic arch. An erroneous diagnosis of mediastinal neoplasm was made. The patient (a girl of 19) was operated on, and the aneurysm was opened with immediately fatal results.

The cause of death in 1 case was pulmonary tuberculosis; in 1, rupture into the pericardium, and in 1, opening, at operation, of the aneurysm, which was mistaken for a neoplasm; in 3 cases, congestive heart failure, and in 3, superimposed infective endarteritis.

(*r*) 90, 101, 118, 269.
(*s*) 101, 175, 292.
(*t*) 33, 118, 269.
(*u*) 175 (2 cases), 309.

At autopsy the heart showed the congenital lesions previously mentioned. In the cases in which the only congenital lesion was in the pulmonary artery itself, the right ventricle was hypertrophied.

The aneurysm usually involved only the stem of the pulmonary artery. In Esser's case,[101] that of a woman of 23, the stem of the pulmonary artery was as thin as paper and formed a thin-walled sac to within 1.5 cm. of the bifurcation, where it suddenly narrowed and became thicker. In Lissauer's [175] first case the pulmonary artery as far as the orifice of the patent ductus (which was also dilated) showed a bulge the size of an egg. Beyond the ductus the artery and both its main branches were greatly narrowed. In his second case the stem showed a bulge the size of a walnut to the left immediately above the cusps. The left pulmonary artery was obliterated, and the right was considerably narrowed. In the other cases reported there was merely fusiform dilatation of the stem of the pulmonary artery with or without dilatation of its main branches.

In cases of patent ductus arteriosus the pulmonary artery is always dilated, probably because of the increased pressure transmitted from the aorta. In 3 of the cases here reported there was infective endarteritis, which perhaps weakened the walls enough to allow further bulging. Lissauer attributed the aneurysms in his cases to the rise in pulmonary blood pressure caused by the narrowing of the main branches, but this is unlikely, as it has been shown that tying the artery to one lung causes little or no permanent rise in the pulmonary arterial pressure. It seems more likely that both in the patients with and in those without patency of the ductus or some other congenital cardiac abnormality, the cause of the aneurysm is weakness (probably congenital) of the wall of the artery, though this was proved only in Esser's case, in which the wall of the aneurysm was extremely thin and deficient in elastic tissue.

4. *Syphilitic Aneurysm.*—Reports of 11 cases have been collected from the recent literature.[v] Nine of the patients were men and 2 women, and the ages ranged from 32 to 58 (average, 48). There was no clinical evidence of syphilis in 3 of these, though the changes noted post mortem were characteristic.

In 1 case [25] there were no circulatory symptoms, and the patient died of progressive dementia. Occasionally [w] repeated hemoptysis was the first symptom, but in most cases the symptoms were merely those of progressive congestive heart failure. In some there was little cyanosis; in others it was so marked that a diagnosis of congenital cardiac disease was made.[236] There was no evidence of mediastinal pressure in

(*v*) 9 (2 cases), 25, 166, 170, 236 (2 cases), 238, 278, 311.

(*w*) 166, 311.

any case. The heart was usually enlarged to the right and left. Often there were no abnormalities on auscultation, or only mitral and basal systolic murmurs, but the pulmonary second sound was sometimes accentuated, and in some cases there were diastolic murmurs to the left of the sternum.[x]

The roentgenograms (taken in 4 cases) showed an enlarged heart and a bulging pulmonary artery. The electrocardiogram (in 2 cases) showed preponderance of the right ventricle. The diagnosis was made (on the basis of the roentgenographic evidence) before death in only 1 case.[166]

Death was usually due to congestive heart failure. In 2 cases it was sudden owing to occlusion of the pulmonary artery by a thrombus [170] and to rupture of a dissecting aneurysm into the pericardium.[236]

At autopsy the heart was always enlarged usually owing to hypertrophy of the right ventricle, occasionally with the left ventricle smaller than normal.[238] At times [311] the left ventricle also was enlarged. Sometimes aortic syphilis with aneurysm or aortic incompetence also was present.[y]

In 4 cases the aneurysm was confined to the stem of the pulmonary artery. In 2 it was fusiform and in 2 saccular. In the others there was aneurysm of one or the other main artery, either with or without involvement of the stem also. The sacs were usually partly or completely occluded by thrombi. Typical microscopic changes of syphilitic mesarteritis were present in all cases in which sufficient details were given, and in 1 case [311] spirochetes were found in the wall.

DISSECTING ANEURYSMS

Reports of 4 cases have been found in the literature, but the much quoted case of Brown [46] may be dismissed, as the rupture was in the aorta and the effused blood merely spread along the adventitia of the pulmonary artery. Arrillaga's [9] case is also doubtful, as it is merely stated that a somewhat dilated pulmonary artery had burst into the pericardium. The 2 other cases were in a man of 33 [90] and a woman of 28.[236] In the first patient, about two weeks before death, there was severe pain in the chest. He returned to work for one day and died in his sleep the same night. The second patient had been told at the age of 12 that she had cardiac disease. She was admitted to the hospital with acute nephritis. The heart was enlarged, and there was a systolic and diastolic murmur in the pulmonary area. She suddenly collapsed and died eight days after admission. At autopsy in both cases the pericardium was found to be full of blood. The right ventricle

(x) 9, 166, 311.

(y) 236, 238, 311.

was hypertrophied. In the first case there was a patent ductus arteriosus. At the bifurcation of the stem of the pulmonary artery the intima and media were torn through, and a dissecting aneurysm had formed and burst into the pericardium. In the second case there were changes that were grossly and microscopically characteristic of syphilis of both main pulmonary arteries. In the stem there was a right angle tear through the intima 2 cm. above the cusps. A dissecting aneurysm had formed from this and had burst into the pericardium.

Dissecting aneurysms of the pulmonary arteries thus appear to be even rarer than those of the aorta. In the 2 cases mentioned they were associated with patency of the ductus arteriosus and syphilitic arteritis, respectively. Dissecting aneurysms of the aorta occur rarely in association with syphilitic aortitis. No report of a case of dissecting aneurysm of the aorta associated with patent ductus arteriosus has been found in the literature. The common cause appears to be a peculiar form of degeneration of the aortic media. This was not described in either of the 2 cases of dissecting aneurysm of the pulmonary artery previously mentioned, but Neuberger,[219] in a case of dissecting aneurysm of the aorta with the characteristic degeneration of the media, observed similar but slighter changes in the unruptured pulmonary artery.

SUMMARY AND CONCLUSIONS

This lengthy survey seems to show that the pulmonary circulation plays an important part both in the physiology and in the pathology of the circulation as a whole, but that this part is, with rare exceptions, passive rather than active. The structure of the pulmonary vessels is such that they cannot be expected to play an important part in the regulation of the circulation through the lungs. The experimental evidence on this point is conflicting as to the nature (if any) of the response of the pulmonary vessels to most forms of nervous and pharmacologic stimuli, and it seems probable that any such responses must be feeble and of little importance in regulating the flow of blood through the lungs. By far the most important influence in regulating the pulmonary circulation is the activity of the heart and particularly the state of balance between the two sides of the heart, an increased output of the right side or a diminished output of the left causing congestion of the lungs and vice versa. Two of the most important symptoms of congestive heart failure, namely dyspnea and cyanosis, are dependent on congestion of the lungs caused in this way. There is no evidence that vasomotor activity of the pulmonary vessels is able to modify the process in any way. Again, the pulmonary circulation has so great a reserve (provided by the ready distensibility of the small pulmonary vessels and the large number of "reserve capillaries" through which blood does not

ordinarily flow) that it is difficult to embarrass it by occluding large branches of the pulmonary artery. Ligature of the artery to one lung causes only slight and transient increase in the pressure in the right ventricle, and the cross-sectional area of the stem of the pulmonary artery must be diminished by 75 per cent before the systemic blood pressure falls and by 90 per cent before death occurs (in acute experiments). No doubt even greater degrees of narrowing could be borne if brought about gradually. This is important evidence against the view, so frequently expressed, that comparatively minor degrees of pulmonary arterial disease are the cause of important changes in the heart and of grave symptoms ultimately resulting in death.

Practically all the varieties of vascular disease occurring in the systemic circulation may be observed also in the pulmonary circulation. Some forms, such as syphilitic arteritis, are less common, and others, such as septic and tuberculous arteritis, are more common than in the systemic circulation. Atherosclerosis is exceedingly common, having been noted microscopically in some degree in 97 per cent of 100 consecutive unselected autopsies. Its incidence is therefore as great, though its degree is not so marked, as in the systemic circulation. Its very frequency makes it difficult to determine etiologic factors, though its severity increases somewhat with age and with conditions thought to be associated with a raised pulmonary arterial pressure, such as cardiac disease or chronic pulmonary disease. These are evidently not the only factors, however, since atherosclerosis, sometimes marked, may occur in young persons with no chronic cardiac or pulmonary disease. Moreover, in chronic disease of the lungs, in which it might be expected that though the pulmonary artery pressure would be raised the pulmonary venous pressure would be lowered, marked venous sclerosis may occur. Again, no constant relationship is found between the thickness of the right ventricle and the degree of pulmonary atherosclerosis. There is no good evidence that even the most marked pulmonary atherosclerosis plays an important part in the production of symptoms in these cases.

A few cases of primary pulmonary arteriosclerosis have been reported in the literature, and 2 further cases have been described. This is a condition in which marked pulmonary arterial lesions of several histologic types are associated with hypertrophy of the right ventricle and ultimately heart failure in the absence of the usual causes of heart failure. It is usually said that the arterial lesions are primary and that the hypertrophy of the right side of the heart and the heart failure are secondary, but for the reasons previously given it is concluded that the vascular lesions are rarely extensive enough in themselves to embarrass the pulmonary circulation seriously and that more probably

they and the hypertrophy of the right side of the heart are manifestations of some common unknown cause.

The concept of Ayerza's disease has in the past dominated the consideration of pulmonary vascular disease. It is shown that this concept has varied continuously since its origination, and that the cases of Ayerza's disease that have been described are indistinguishable from cases of failure of the right side of the heart secondary to chronic pulmonary disease and are associated with fairly marked pulmonary atherosclerosis. There seems to be nothing to be gained by retaining the term.

Thrombi, whether embolic or formed in situ, are common in the pulmonary circulation, being found in 28 of 100 consecutive unselected autopsies. They ultimately become completely organized. They rarely cause symptoms unless a large branch of the pulmonary artery is suddenly blocked. The lungs appear to form a filter in the course of the circulation in which solid particles of clot, tumor, fat and other substances are trapped and prevented from entering the systemic circulation.

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EFFECT OF THEOPHYLLINE ETHYLENEDIAMINE ON EXPERIMENTALLY INDUCED CARDIAC INFARCTION IN THE DOG

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Until recent years the various xanthine derivatives were employed in the treatment of cardiac disease chiefly because of their diuretic action. The discovery that these preparations cause dilatation of the coronary arteries and the introduction of theophylline ethylenediamine in 1908 [1] led to a further study of this particular pharmacologic action.

Eppinger and Hess [2] observed a stretching of strips of coronary arteries when they were placed in a solution of caffeine, and Gow,[3] employing a similar method, noted a dilatation of arterial rings taken from the renal and splenic arteries. Hedbom [4] was among the first to study the problem by the perfusion method and reported an increase in the coronary flow with caffeine in a concentration of 1 : 20,000. Loeb [5] observed a marked increase in the rate of perfusion with theobromine but very little effect with caffeine. Heathcote,[6] working with caffeine, theobromine and theophylline in concentrations from 1 : 2,000 to 1 : 40,000, obtained a marked increase in the rate of perfusion with the higher concentrations, but in dilutions of 1 : 20,000 and 1 : 40,000 caffeine

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1. Dessauer, P.: Euphyllin, neues Diuretikum, Therap. Monatsh. **22**:401, 1908.

2. Eppinger, H., and Hess, L.: Versuche über die Einwirkung von Arzneimitteln auf überlebende Coronargefässe, Ztschr. f. exper. Path. u. Therap. **5**:622, 1909.

3. Gow, D.: Some Reactions of Surviving Arteries, J. Physiol. **42**:125, 1911.

4. Hedbom: Skandinav. Arch. f. Physiol. **9**:1, 1899; cited in Therapeutic Claims for Theobromine and Theophyllin Preparations, report of the Committee on Pharmacy and Chemistry, J. A. M. A. **94**:1306 (April 26) 1930.

5. Loeb, O.: Ueber die Beeinflussung des Koronarkreislaufs durch einige Gifte, Arch. f. exper. Path. u. Pharmakol. **51**:64, 1904.

6. Heathcote, R. St. A.: The Action of Caffeine, Theobromine and Theophylline on the Mammalian and Batrachian Heart, J. Pharmacol. & Exper. Therap. **16**:327, 1920.

produced no change, theobromine very little and theophylline from 20 to 30 per cent increase. Guggenheimer and Sassa,[7] using the isolated heart of a cat, found that caffeine in a dilution of 1:25,000 increased the rate of perfusion 41 per cent. Theophylline and theophylline ethylenediamine in similar concentrations produced an increase of 40 and 80 per cent, respectively. More recently, Smith, Miller and Graber [8] studied the effects of certain of these drugs by perfusion experiments on the isolated heart of a rabbit. Caffeine sodiobenzoate in a concentration of 1:25,000 did not produce a significant change in the rate of perfusion. Theobromine sodiosalicylate in the same concentration did not produce a change, but when a concentration of 1:50,000 was employed a slight increase in the rate of perfusion was noted. Theophylline in concentrations of 1:25,000 and 1:50,000 augmented the coronary flow from 20 to 45 per cent, while theophylline ethylenediamine in similar concentrations increased the rate of flow from 40 to 90 per cent.

These aforementioned investigators subsequently studied the action of theophylline and theophylline ethylenediamine on the intact dog by means of the Morowitz-Zahn cannula and obtained comparable results.[9] Various other workers have employed the intact animal in the investigation of this problem. Meyer,[10] recording the flow from a coronary vein, reported that the intravenous administration of caffeine is followed by an increase in the rate of coronary flow, but he attributed this result to an elevation in the systemic blood pressure. Sakai and Saneyoshi,[11] from experiments on the intact heart in which they employed the Morovitz-Zahn cannula, obtained an increased flow with average and large doses of theobromine sodiosalicylate.

Fisher, Guggenheimer and Müller,[12] working with the heart-lung preparation, studied the action of theophylline ethylenediamine,

7. Guggenheimer, H., and Sassa, K.: Ueber die Beeinflussung des Coronarkreislaufs durch Purinderivate, Klin. Wchnschr. **2**:1451, 1923.

8. Smith, F. M.; Miller, G. H., and Graber, V. C.: The Effects of Caffeine Sodiobenzoate, Theobromin Sodiosalicylate, Theophyllin and Euphyllin on the Coronary Flow and Cardiac Action of the Rabbit, J. Clin. Investigation **2**:157, 1925.

9. Smith, F. M., and Miller, G. H.: The Study of the Action of Theophyllin and Theobromine on the Coronary Circulation of the Intact Heart, Am. J. Physiol. **85**:407, 1928.

10. Meyer, F.: Ueber die Wirkung verschiedener Arzneimittel auf die Coronargefässe des lebenden Tieres, Arch. f. Physiol., 1912, p. 223.

11. Sakai, S., and Saneyoshi, S.: Ueber die Wirkung einiger Herzmittel auf die Koronargefässe, Arch. f. exper. Path. u. Pharmakol. **78**:331, 1915.

12. Fisher, I.; Guggenheimer, H., and Müller, E. A.: Ueber die Beeinflussung von Koronardurchblutung und Herztonus durch Theophyllinpräparate und Strophanthin nach Untersuchungen am Starlingschen Herz-Lungenpräparat, Deutsche med. Wchnschr. **54**:1584, 1928.

theophylline and strophanthin. There was a distinct increase in the rate of coronary flow after the administration of theophylline ethylenediamine and theophylline, whereas a decrease was noted after the administration of strophanthin. More recently, Gilbert and Fenn,[13] using the intact animal, found theobromine and its salts to be the most effective and caffeine sodiobenzoate the least effective in increasing the coronary flow. Intermediate effects were obtained with theophylline ethylenediamine and theophylline sodio-acetate.

Because of the discrepancy in the results obtained by various investigators and as a preliminary step to the further study of this question, the perfusion experiments on the isolated heart of the rabbit were repeated. It is to be noted in the table that of the various preparations

The Percentage Increase in the Coronary Flow with the Various Preparations *

	Dilution			
	1:15,000	1:25,000†	1:30,000	1:60,000
Glycocyamine	.....	18.21	35.32	15.38
Caffeine sodiobenzoate	.....	.....	20.53	.....
Sodium nitrite	.....	62.91	.....	.....
Theobromine sodio-acetate	.....	42.87	32.14	.....
Theophylline sodio-acetate	.....	.....	29.18	.....
Theophylline mono-ethanolamine	27.35	51.13	38.46	11.21
Theophylline ethylenediamine	.....	96.65	38.8	.....
Sodium nitrite 1:50,000 and theophylline ethylenediamine 1:25,000				81.98
Glycocyamine 1:50,000 and theophylline ethylenediamine 1:25,000				56.07
Glycocyamine 1:50,000 and theobromine sodio-acetate 1:50,000				32.22

* The figures represent the average increase obtained in from two to twenty trials.
† An intravenous preparation of theophylline ethylenediamine was used in the 1:20,000 dilution, whereas the tablet form was used in the 1:30,000 dilution.

employed, theophylline ethylenediamine was by far the most effective. The augmentation of the coronary flow was usually associated with an increase in the rate and amplitude of cardiac contraction, but there was no definite correlation between the increased amplitude and the increase in coronary flow. Moreover, it has been shown [8] that the increase in the cardiac rate does not appreciably affect the rate of perfusion. Of the various drugs employed, theophylline ethylenediamine had the most beneficial effect on the myocardium, as evidenced by the disappearance of irregularities in certain instances and an increase in the amplitude of cardiac contraction. Combinations of various drugs were tried, but these were no more effective than theophylline ethylenediamine alone. In view of the aforementioned results, theophylline ethylenediamine was selected for a more decisive test of its dilating action on the coronary vessels.

13. Gilbert, N. C., and Fenn, G. K.: The Effect of the Purine Base Diuretics on the Coronary Flow, Arch. Int. Med. **44**:118 (July) 1929.

EXPERIMENTAL OBSERVATIONS

Immediate Effects.—Six dogs were utilized in a study of the immediate effects of theophylline ethylenediamine on the coronary circulation. Ethyl carbamate (urethane) supplemented by a small amount of ether served as the anesthetic, and artificial respiration was maintained by intermittent positive pressure through a tracheal catheter. A continuous record of the blood pressure was obtained from the carotid artery. The thoracic wall was incised, and the pericardium was opened. The edges of the pericardial slit were sutured to those of the thoracic incision, forming a support for the heart. The anterior descending branch of the left coronary artery, together with the accompanying vein, was ligated just above the origin of the last main branch. Almost immediately an area of cyanosis appeared distal to the ligation. This gradually increased in size and reached its maximum extent in about five minutes. Theophylline ethylene-

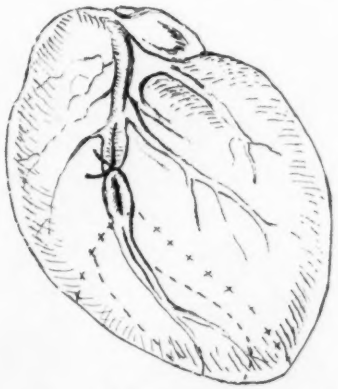

Fig. 1.—The crisscross line indicates the outline of the cyanotic area immediately after ligation of the coronary vessels. The line of dashes represents the outline of the cyanotic area after the intravenous administration of theophylline ethylenediamine.

diamine was then administered intravenously, and the effects on the cyanosis and blood pressure were noted.

In the first three animals 2 cc. (0.48 Gm.) of the drug was injected into the femoral vein. A change in the area of cyanosis was apparent within two minutes after the injection, and the maximum effect was reached within five minutes. The edges of the cyanotic area, which prior to the administration of the drug had been sharply defined, became blurred, indistinct and irregular and gradually receded toward the ligated vessel. The extent to which the area of cyanosis disappeared varied from animal to animal, but from 50 to 90 per cent of the cyanosed area was restored to normal color in each instance and became indistinguishable from the uninvolved surrounding area. In the two animals showing the most striking regression the wall of the left ventricle was almost completely cleared of cyanosis, and the only remaining discoloration was confined to a small area on the wall of the right ventricle adjacent to the ligated vessel. The disappearance of the cyanosis was associated with a rather prompt drop in the blood

pressure ranging from 40 to 55 mm. of mercury. There was little tendency for the blood pressure to return to the original level.

In the fourth animal there was a striking reduction in the extent and degree of cyanosis, accompanied by a drop in blood pressure from 102 to 55 mm. Injection of hypertonic solution of dextrose (40 cc. of a 50 per cent solution) was followed by a return of the blood pressure to approximately the original level without a reappearance of the cyanosis.

In the remaining two animals theophylline ethylenediamine was diluted in a 50 per cent solution of dextrose and introduced slowly and intermittently over a period of thirty minutes. After each small injection the blood pressure dropped from 6 to 12 mm. but returned promptly to the original level. By this method of administration there was a striking reduction in the area of cyanosis, while the blood pressure was maintained at approximately a constant level. After reduction of the cyanosis by the administration of theophylline ethylenediamine, epi-

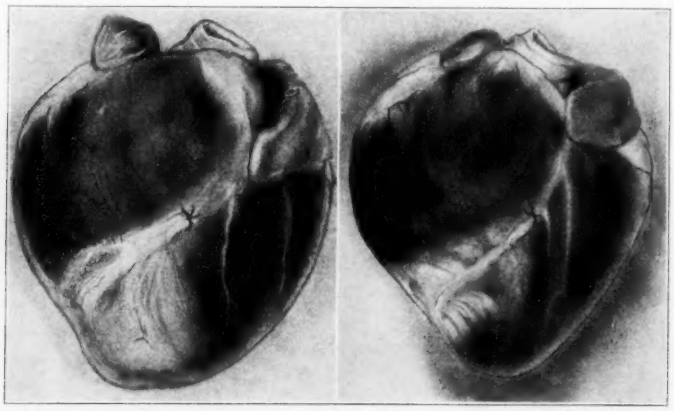

Fig. 2.—Drawings showing the size of the myocardial infarction in the control animals at the end of three weeks.

nephrine (0.2 cc. of a 1:1,000 solution) was given intravenously. There was a prompt elevation of the blood pressure, with a return of the area of cyanosis to its original extent. The area of cyanosis was again dispersed by the injection of theophylline ethylenediamine. At the termination of these experiments, about one and one-half hour after the ligation of the vessel, the blood pressure was within 12 mm. of the original level, and about 75 per cent of the area of cyanosis had been restored to normal color.

Late Effects.—In nineteen dogs the anterior descending limb of the left coronary artery was ligated just below the origin of the last main branch. Slight variations in the arterial distribution were encountered in a few instances, but the ligature was placed as nearly as possible at a constant level. The dogs were examined at autopsy three weeks after the operation, and the extent of the myocardial infarction was carefully studied. The first ten of these animals served as controls, whereas the remaining nine were given theophylline ethylenediamine, 3 grains (0.195 Gm.) daily, after the operation.

In the ten control animals the coronary artery was found to be completely occluded in all instances, with a resultant area of myocardial fibrosis distal to the ligation. The infarct began immediately below the ligature and extended to the apex and in most instances beyond this point to the posterior wall of the left ventricle. The infarct gradually increased in width, reaching its maximum a short distance above the apical region. The wall of the left ventricle bore the brunt of the injury in all instances, but the adjacent wall of the right ventricle was always involved to some extent. The interventricular septum was invaded by fibrous tissue to a varying degree in each animal. The outline of the infarcted area was irregular and presented a frayed-out or fringelike appearance, due to the extension of fine streaks of fibrous tissue into the surrounding musculature. The endocardium immediately beneath the area of greatest myocardial damage presented a whitish discoloration. In seven of the ten animals the wall of the left ventricle near the apex was greatly diminished in thickness, and the muscu-

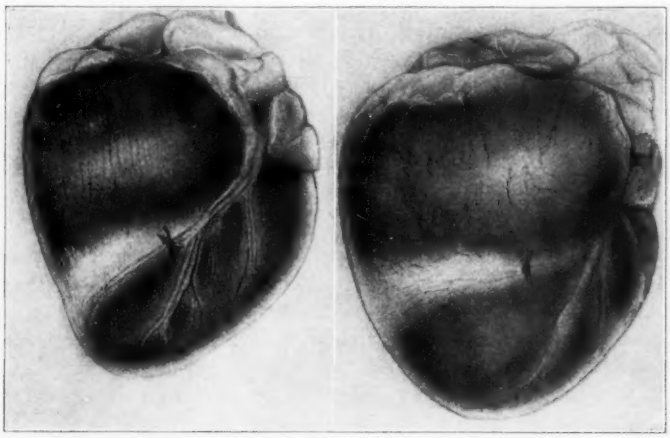

Fig. 3.—Drawings showing the size of infarction at the end of three weeks in the dogs that received theophylline ethylenediamine.

lature consisted entirely of fibrous tissue. In the other three dogs the replacement of fibrous tissue appeared just as extensive, although there was no evident reduction in the thickness of the wall.

Nine animals were given theophylline ethylenediamine, 3 grains daily, throughout the postoperative course. In one of these the coronary artery was not completely occluded, and the heart was discarded. In two animals the drug was injected intramuscularly, and sterile abscesses developed at the site of injection. Although the absorption was probably incomplete in these animals, the extent of the infarction was considerably less than that in the control series. They presented, however, a rather extensive fibrosis. In the remaining six animals the drug was given by mouth, first by a stomach tube for a few days immediately following the operation and later concealed in a bit of food. The area of fibrosis was markedly diminished and was a narrow strip parallel to the course of the ligated vessel, with no tendency to increase in width as it approached the apex. The length of the infarcted area was distinctly reduced, as it never extended

beyond the apex and in most cases disappeared proximal to this point. The outline of the infarct was sharply demarcated, with few strands of fibrous tissue extending into the adjacent musculature. In no instance was there a demonstrable reduction in the thickness of the wall of the left ventricle, and on cut section the myocardium of this chamber presented a surprisingly normal appearance. The extent of involvement in the interventricular septum was greatly reduced, and there were instances in which there was no apparent endocardial involvement. The extent of fibrosis on the wall of the right ventricle was reduced but slightly, so that this region presented the most extensive damage in this group of animals. It is of interest that this area corresponded exactly with the area of persistent cyanosis in the preceding experiment.

COMMENT

The effects of theophylline ethylenediamine on the coronary circulation has been demonstrated by the increased rate of perfusion in the isolated heart of the rabbit, by the regression of the area of cyanosis appearing immediately after the ligation of a coronary vessel in the dog and, finally, by the marked reduction in the extent of fibrosis in survival experiments. There are obvious objections to the perfusion method of testing the action of drugs on the coronary circulation, but the observations on the intact heart in the foregoing experiments in our opinion demonstrate conclusively the dilating action of theophylline ethylenediamine.

The extent of the cardiac infarction in cases of coronary occlusion is determined by the size of the vessel occluded and the effectiveness of the collateral circulation. It is apparent that treatment should be directed toward the restoration of the circulation to the damaged area. In the experiments reported here the changes observed both as to early and as to late effect were no doubt dependent on the action of the drug on the collateral circulation. While in the experimental animal we were dealing with normal vessels, the character of the results obtained recommended the use of theophylline ethylenediamine in the treatment of acute coronary occlusion. Our clinical results so far are in accord with what might be expected from the experimental study.

In order to conserve the cardiac musculature of the infarcted area to the maximum extent through the development of the collateral circulation, the medication should be employed early in the course of acute coronary occlusion and should be continued until there is sufficient time for the infarct to heal. Intravenous administration of the drug, for at least the initial dose, insures a more prompt response and in certain instances is justifiable. In our experience the slow administration of the drug ordinarily prevents any untoward effects from a reduction in the blood pressure. Experimental observations indicate that the combination with hypertonic solution of dextrose may provide an additional safeguard against this possibility.

CONCLUSION AND SUMMARY

The experiments reported here have demonstrated that theophylline ethylenediamine promotes the development of the collateral circulation in experimentally induced cardiac infarction in the dog. The results justify the use of this preparation in the treatment of disease of the coronary arteries and acute coronary occlusion.

THEOPHYLLINE IN THE TREATMENT OF DISEASE OF THE CORONARY ARTERIES

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The reduction in the coronary circulation through the gradual encroachment on the lumen due to sclerotic changes and, finally, the occlusion of vessels of varying size is primarily responsible for the cardiac disability in disease of the coronary arteries. It is thus important that treatment be directed toward the restoration and maintenance of an effective coronary circulation in this form of cardiac disease. Various remedies, particularly the xanthine derivatives, have been recommended for this purpose. In a previous communication [1] experimental data concerning the effectiveness of these preparations were reviewed, and additional observations relative to the dilating action of theophylline ethylenediamine were reported. The latter experiments in our opinion conclusively demonstrated the dilating action of this preparation on the coronary arteries of the dog.

The xanthine derivatives are well known for their diuretic action, and it is generally conceded that theophylline is the most effective of the group. Marvin [2] has shown that the diuretic action of xanthine derivatives is most marked in cases of congestive failure of arteriosclerotic cardiac disease. It would seem, as suggested by one of us in a previous report,[3] that the effectiveness of the preparations under the aforementioned conditions is probably enhanced by the improvement in the function of the myocardium through the dilating action on the coronary vessels.

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Presented at the Tenth Scientific Session of the American Heart Association, Cleveland, June 12, 1934.

1. Fowler, W. M.; Hurevitz, H. M., and Smith, Fred M.: The Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction, Arch. Int. Med., this issue, p. 1242.

2. Marvin, H. M.: The Value of the Xanthine Diuretics in Congestive Heart Failure, J. A. M. A. **87**:2043 (Dec. 18) 1926.

3. Smith, Fred M.: The Diet and Theophyllin in the Treatment of Cardiac Failure, J. A. M. A. **91**:1274 (Oct. 27) 1928.

Askanazy [4] was apparently the first to recommend the use of the xanthine derivatives in disease of the coronary arteries, having observed favorable results from the employment of theobromine sodiosalicylate in cases of angina pectoris and occasionally striking improvement in patients with cardiac asthma, with or without anginal pain. These results were later confirmed by Breuer,[5] who particularly emphasized the importance of this remedy in the treatment of angina pectoris and cardiac asthma. Dessauer [6] in 1908 introduced theophylline ethylenediamine and reported striking diuretic action in patients with congestive cardiac failure. The addition of ethylenediamine to theophylline produced a more soluble and less irritating combination. Guggenheimer [7] observed favorable results from the use of theophylline ethylenediamine in patients with arteriosclerotic cardiac disease without edema, which he was inclined to attribute to the probable dilating action on the coronary vessels. This led to the experimental investigation of this feature by Guggenheimer and Sassa.[8]

The widespread interest in diseases of the coronary arteries during recent years again directed attention to the xanthine derivatives and stimulated further experimental and clinical study of the action of these preparations on the coronary vessels. Certain of these experimental studies were reviewed in the previous communication.[1] In the meantime, clinical reports by Smith, Miller and Graber,[9] Dock,[10] Musser,[11] Vogl,[12] Gilbert and Kerr,[13] Guggenheimer [14] and others appeared in the

4. Askanazy, S.: Klinisches über Diuretin, Deutsches Arch. f. klin. Med. **56**:209, 1895.

5. Breuer, R.: Zur Therapie und Pathogenese der Stenokardie und verwandte Zustände, München. med. Wchnschr. **49**:1604, 1902.

6. Dessauer, P.: Euphyllin ein neues Diuretikum, Therap. Monatsh. **22**:401, 1908.

7. Guggenheimer, H.: Zur Herzbehandlung bei Erkrankungen der Koronargefässe, Deutsche med. Wchnschr. **49**:1007, 1923.

8. Guggenheimer, H., and Sassa, K.: Ueber die Beeinflussung des Coronarkreislaufs durch Purinderivate, Klin. Wchnschr. **2**:1451, 1923.

9. Smith, Fred M.; Miller, G. H., and Graber, V. C.: The Study of the Action of Euphyllin in Cardiac Failure Associated with Arteriosclerosis, Tr. Sect. Pharmacol. & Therap., A. M. A., 1926, p. 171.

10. Dock, William: The Use of Theobromine for Pain of Arteriosclerotic Origin, California & West. Med. **25**: 636, 1926.

11. Musser, J. H.: Theophylline-Ethylenediamine in Heart Disease Associated with Pain, J. A. M. A. **91**:1242 (Oct. 27) 1928.

12. Vogl, A.: Erfahrungen über Euphyllin bei Cheyne-Stokes und anderen Formen zentraler Atemstörungen, Med. Klin. **28**:9, 1932.

13. Gilbert, N. C., and Kerr, John Austin: Clinical Results in Treatment of Angina Pectoris with the Purine Base Diuretic, J. A. M. A. **92**:201 (Jan. 19) 1929.

14. Guggenheimer, H.: Ueber die Wirkungsweise des Euphyllins bei kardiovasculärem Cheyne-Stokes und Asthma cardiale, Ztschr. f. Kreislaufforsch. **25**: 98, 1933.

literature. These observations were concerned with the effectiveness of theophylline, chiefly in the form of theophylline ethylenediamine or the preparations of theobromine, for patients with angina pectoris or paroxysmal dyspnea. In certain instances in each of these series, favorable or even striking results were obtained. The report by Gilbert and Kerr, based on the study of 86 cases of angina pectoris, is of particular significance in that the patients were ambulatory and were permitted to continue with their regular activities and no other medication was employed. Observations were made on the effect of preparations of theobromine, theophylline and theophylline ethylenediamine. These observers were careful in the interpretation of their results, realizing the marked variation in the clinical course of the disorder and the variety of means by which it may be influenced. In this series of 86 cases there were only 14 patients who obtained no relief from any preparation used. The remaining 72 showed varying degrees of improvement.

In this communication we wish to report our experience covering a period of eight years with the use of theophylline and theophylline ethylenediamine in the treatment of disease of the coronary arteries, manifested by congestive failure, paroxysmal dyspnea, angina on effort or occlusion of the coronary arteries. The preparations of theophylline were employed exclusively, because in the experimental study made by Smith, Miller and Graber,[9] on both the isolated and the intact heart, these substances had a more pronounced action on the coronary circulation than the other xanthine derivatives.

These preparations were prescribed as a routine in the treatment of congestive failure, not only because of their diuretic action but because of their favorable influence on the coronary circulation. The onset of the cardiac disability in cases of disease of the coronary arteries is commonly marked by shortness of breath, followed in time by congestive failure. Of a series of 420 cases reported [15] this type of onset occurred in 189.

From 1½ to 3 grains (97.2 to 194.4 mg.) of theophylline ethylenediamine three times a day is usually prescribed. From 2 to 3 grains (129.6 to 194.4 mg.) of theophylline three times a day, however, is frequently used, and it may be combined with theophylline ethylenediamine when a more pronounced diuretic action is desired. Occasionally in the cases of greater urgency, especially in the presence of nausea and vomiting, 480 mg. of theophylline ethylenediamine is administered intravenously once or twice daily.

15. Smith, Fred M.; Rathe, Herbert W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, J. A. M. A. **105**:2 (July 6) 1935.

RESULTS IN CASES OF CONGESTIVE FAILURE

The following reports of cases illustrate the action of the theophylline in the treatment of congestive failure due to disease of the coronary arteries. Digitalis was withheld, and only the cases of congestive failure in advanced stages were selected, in order to test the effectiveness of the medication.

CASE 1.—E. J., aged 67, was admitted to the University Hospital on Nov. 2, 1930, complaining of shortness of breath and swelling of the legs. Shortness of breath was first noticed in December 1929, and edema of the ankles in September 1930. The patient presented advanced congestive failure with marked orthopnea and cyanosis. The heart was very large, and the rhythm irregular, owing to auricular fibrillation. The blood pressure measured 140 systolic, and 90 diastolic.

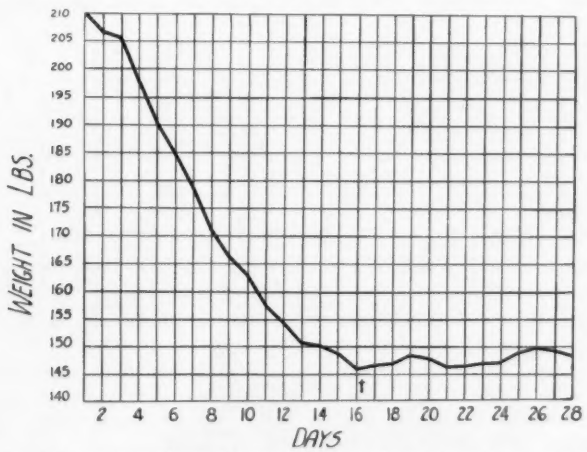

Chart 1 (case 1).—Curve showing the loss of weight after administration of theophylline in a case of congestive failure due to disease of the coronary arteries. The dagger indicates the point at which digitalis was prescribed.

Examination of the urine showed traces of albumin and occasional hyaline and granular casts. The teleoroentgenogram revealed that the transverse diameter of the heart measured 19 cm. and one pulmonary field, 14 cm. The electrocardiogram showed left axis deviation, auricular fibrillation, slurring of the ventricular complexes and an inverted T wave in lead 1.

The patient was given rest in bed, a cardiac diet, ½ grain (32.4 mg.) of phenobarbital after meals and at bedtime, liquid petrolatum at night and in the morning, ¼ grain (16.2 mg.) of morphine sulfate hypodermically at bedtime, which was to be repeated if necessary to induce sleep but was discontinued after the third night, and 2 grains of theophylline three times a day. On the seventeenth day 15 minims (0.924 cc.) of tincture of digitalis three times a day was prescribed.

The curve in chart 1 shows the rapid loss in weight observed in this patient. It is to be noted that the weight decreased from 210 to 146 pounds (95.2 to

66.3 Kg.) in sixteen days. At this time digitalis was prescribed, and its administration was continued throughout the remainder of the stay in the hospital.

Case 2.—Mrs. E. R., aged 66, was admitted to the University Hospital on May 9, 1930, because of congestive heart failure. She had been in the hospital in July 1929 for the same condition. The present attack began in March 1930. The patient presented the usual signs of advanced congestive failure. The heart was enlarged. The teleoroentgenogram revealed the transverse diameter of the heart to be 18 cm. and one pulmonary field, 13.1 cm. The blood pressure measured 145 systolic and 88 diastolic. The electrocardiogram showed slurred ventricular complexes of low amplitude and an iso-electric T wave in all the leads.

Treatment consisted of rest in bed, a cardiac diet, liquid petrolatum, ½ grain (32.4 mg.) of phenobarbital after meals and at bedtime, and ¼ grain (16.2 mg.) of morphine sulfate given hypodermically at bedtime. There was no appreciable change in the condition of the patient for six days, except that

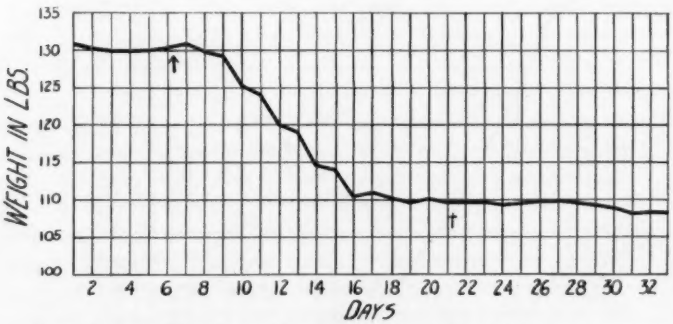

Chart 2 (case 2).—Curve showing the loss of weight after treatment with theophylline in a case of congestive failure. The arrow indicates the point at which the administration of theophylline was begun; the dagger, that at which the medication was supplemented by digitalis.

she was relaxed and slept well during the night. At this point 3 grains of theophylline three times a day was prescribed.

It is to be noted from the curve in chart 2 that the administration of theophylline was soon followed by loss in weight, which continued until the edema was entirely eliminated. This was accompanied by prompt improvement in the general condition of the patient. The treatment just outlined was supplemented by the use of digitalis on the twenty-first day.

Case 3.—O. P., aged 58, was admitted to the University Hospital on Aug. 25, 1933, because of congestive failure and diabetes. There was a history of diabetes for twenty years. An attack of congestive failure occurred two years before, and there had been shortness of breath since that time. Ten days after admission a severe attack of substernal pain occurred, lasting several hours, followed by congestive failure.

The patient suffered from extreme dyspnea and presented extensive edema. The heart was moderately enlarged, both to the right and to the left. The teleoroentgenogram revealed that the transverse diameter of the heart measured 16 cm. and one pulmonary field, 14 cm. The urine contained albumin, sugar and

casts. The blood sugar content was 221 mg. per hundred cubic centimeters. The electrocardiogram showed ventricular complexes of low voltage and an inverted T wave in leads II and III.

The treatment consisted of rest in bed, a cardiac diet, 7 units of insulin three times a day, liquid petrolatum, ¼ grain (16.2 mg.) of morphine sulfate given hypodermically at bedtime and 1½ grains of theophylline ethylenediamine three times a day. On the fifth day 2 grains of theophylline three times a day was added.

The curves for weight, vital capacity and venous pressure and the graph representing the output of urine are shown in chart 3. There was no significant change in any of these values until after administration of theophylline was begun, on the fifth day. It is to be noted that after this medication was begun the response was prompt.

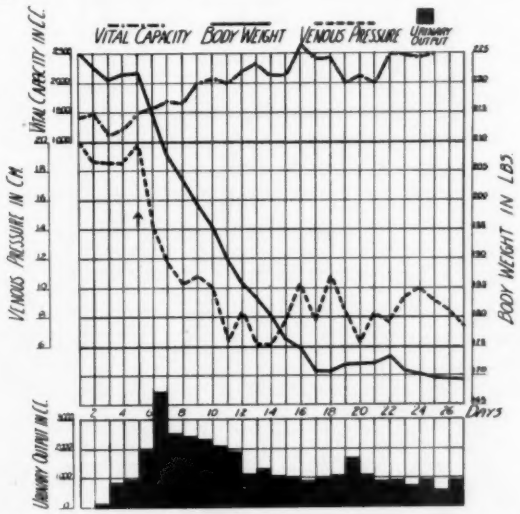

Chart 3 (case 3).—Curves for weight, vital capacity and venous pressure and a graph showing the output of urine in a case of congestive failure in which theophylline was used. The arrow indicates the point at which medication with theophylline ethylenediamine was begun.

CASE 4.—L. K., aged 64, was admitted to the University Hospital on Jan. 12, 1933, for the third time for the treatment of congestive failure. On each previous admission it had been difficult to restore the cardiac function, and during the second stay in the hospital salyrgan was finally administered to eliminate edema. The patient was again in a state of advanced cardiac failure. The heart was very large. The teleoroentgenogram revealed that the transverse diameter of the heart measured 20 cm. and one pulmonary field, 14 cm. The rhythm was irregular, owing to auricular fibrillation. The blood pressure measured 220 systolic and 130 diastolic. The electrocardiogram showed auricular fibrillation and an inverted T wave in leads I and II.

Treatment consisted of rest in bed, a cardiac diet, liquid petrolatum, morphine sulfate as necessary for sleep at night and 3 grains of theophylline ethylenediamine three times a day.

The curves for weight, venous pressure and vital capacity and the graph representing the output of urine are shown in chart 4. No appreciable change in any of these findings appeared until the seventh day. At this point appeared an increase in the output of urine, a reduction of 4 pounds (1.8 Kg.) in weight and increase in the vital capacity. On the eighth day venesection with the removal of 500 cc. of blood was performed. After this, there was a marked increase in the output of urine, accompanied by an abrupt reduction in weight and venous pressure and prompt improvement in the vital capacity.

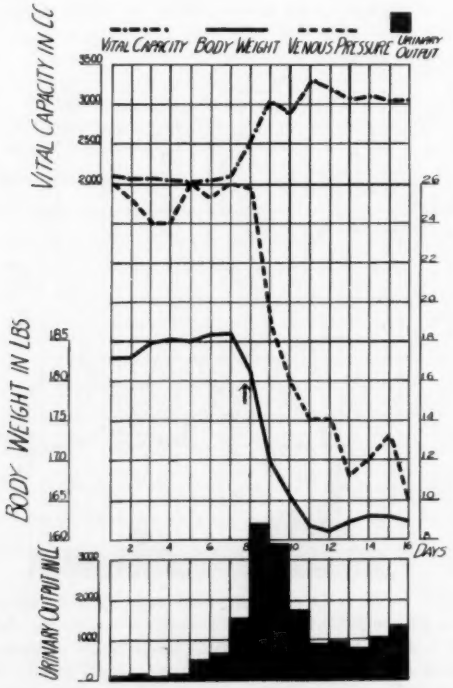

Chart 4 (case 4).—Curves for weight, vital capacity and venous pressure and a graph showing the output of urine in a case of congestive failure in which theophylline ethylenediamine was used. The arrow indicates the point at which a venesection was performed.

Comment.—The preparations of theophylline are among the most effective remedies in the treatment of congestive failure due to disease of the coronary arteries. The action is prompt and generally evident in all cases in which it is possible to restore the cardiac function, provided the work of the heart is reduced to the minimum through absolute rest in bed, relaxation and sleep. Occasionally, it may be necessary to increase the dosage, as illustrated in case 3. In the more advanced

forms of congestive failure the utilization of other available means of reducing the work of the heart, such as aspiration of excess fluid from the peritoneal and pleural cavities and venesection, may have a significant influence on the subsequent course, as shown in case 4.

In routine practice we usually prescribe digitalis in conjunction with theophylline ethylenediamine in the treatment of congestive failure resulting from disease of the coronary arteries. Digitalis is usually employed in the form of the powdered leaf, 1½ grains from three to four times a day being given. After from three to five days the number of doses is reduced to one or two a day. When the patient is discharged from the hospital he is usually advised to continue the treatment with from 1 to 1½ grains (64.8 to 97.2 mg.) daily. Occasionally, it may be necessary to increase the dosage if there is auricular fibrillation. The combination of digitalis in small amounts and theophylline is apparently more effective than either drug alone. We do not believe, however, that digitalis in large amounts is necessary, and it may even retard the progress. Certain of our patients have shown prompt improvement after the use of digitalis was discontinued and theophylline was prescribed.

Theophylline, generally in the form of theophylline ethylenediamine, 1½ grains after meals, is continued after the patient leaves the hospital. This method of administration promotes the development of more efficient cardiac function and postpones the recurrence of symptoms. Patients, in reporting on their progress, have usually stated that they felt much better while on the medication, or on returning to the hospital because of recurrence of congestive failure they have often told us that they were free from symptoms during the time that they were taking theophylline ethylenediamine.

RESULTS IN CASES OF PAROXYSMAL DYSPNEA, ANGINA ON EFFORT AND OCCLUSION OF THE CORONARY ARTERIES

The results in 100 cases of paroxysmal dyspnea, angina on effort and occlusion of the coronary arteries in which treatment was administered outside the hospital are shown in the table. A large majority of the patients have been observed for more than one year, and some for three or four years. In all except a few instances theophylline was the only medicament employed for the cardiac disease. It was usually prescribed in doses of 1½ grains three times a day, and was continued for a long period. The following cases are illustrative of those in which a favorable response was shown.

CASE 1.—Mrs. E. L. K., aged 68, was first examined on Aug. 4, 1932. She presented a history of shortness of breath and occasional angina on effort for two years. The angina had been more frequent and severe during the months prior to examination. The heart was slightly enlarged; there were no murmurs,

and the sounds were of good quality. The blood pressure measured 110 systolic and 88 diastolic. The electroardiogram showed an S wave in lead I, a Q wave in lead III and notching of the QRS group.

The patient took theophylline for six weeks and obtained marked relief, and the medication was then discontinued. The symptoms returned in two weeks. She again took theophylline with resulting relief. She repeated this experience several times with the same results. She was last observed on April 5, 1933, and at the time of writing she was taking theophylline regularly.

CASE 2.—F. A. O., aged 71, was first examined on April 14, 1933. There was a history of shortness of breath on exertion and angina on effort for eight years. Occlusion of a coronary artery with progressive changes in the T wave occurred on April 12, 1933. The heart was enlarged, and the sounds were muffled. The blood pressure measured 128 systolic and 74 diastolic.

Rest in bed and theophylline were prescribed for eight weeks. The medication was discontinued after the patient was up and about. Dyspnea and angina returned, and the symptoms disappeared after resumption of medication. This patient also repeated the experience several times. During the past twelve months, however, he has taken theophylline regularly, and during this time he has been free from cardiac symptoms.

CASE 3.—J. G. P., aged 54, was first examined on April 25, 1933. There was a history of shortness of breath for several months. Shortly before examination

Results of Treatment with Theophylline in One Hundred Cases of Paroxysmal Dyspnea, Angina of Effort and Occlusion of the Coronary Arteries

	Number of Cases	Results		
		Favorable	Questionable	Negative
Paroxysmal dyspnea	20	13	2	5
Angina of effort	25	19	2	4
Occlusion of the coronary arteries	55	40	7	8
Total number of cases	110	72	11	17

the patient experienced several attacks of paroxysmal dyspnea, accompanied by a sense of substernal constriction. The heart was enlarged and a gallop rhythm was heard. The blood pressure measured 190 systolic and 120 diastolic. The electrocardiogram revealed bundle branch block. Theophylline was prescribed, and the patient was permitted to continue with the usual activities. He has received medication for one year and is free from symptoms.

CASE 4.—C. C. S., aged 65, was first examined on May 10, 1931. He gave a history of being short of breath on exertion for two years. For six months prior to examination he had had numerous attacks of paroxysmal dyspnea. The heart was enlarged, and gallop rhythm and a systolic apical murmur were noted. The blood pressure measured 150 systolic, and 80 diastolic. The electrocardiogram revealed bundle branch block.

After taking theophylline, the patient was able to be more active. He noticed that when medication was discontinued dyspnea returned. He has taken theophylline regularly for three years.

CASE 5.—L. B., aged 62, was first examined on May 9, 1931. He gave a history of occlusion of a coronary artery two months before, followed by shortness of breath on slight exertion. The heart was enlarged, and the cardiac sounds were of poor quality. The blood pressure measured 160 systolic and

110 diastolic. The electrocardiogram showed progressive changes in the T wave. Even though this patient continued work as a clerk, dyspnea disappeared after taking theophylline. He has been receiving medication for two years, and during this time he has not curtailed his activities.

CASE 6.—J. D. T., aged 61, was first examined on Jan. 10, 1933. There was a history of angina on effort for six months and occlusion of a coronary artery two months after the onset. The blood pressure measured 110 systolic, and 76 diastolic. The electrocardiogram showed the usual changes in the T wave. The patient was given rest in bed, and theophylline was prescribed for two months. Medication was discontinued on several occasions, and on each trial dyspnea returned but disappeared on the resumption of medication. The patient is now taking theophylline regularly.

CASE 7.—R. W., aged 64, was first examined on July 8, 1932. There was a history of occlusion of a coronary artery three months before and of shortness of breath and nocturnal dyspnea for six weeks. The heart was moderately enlarged, and the cardiac sounds were poorly differentiated. The blood pressure measured 122 systolic and 88 diastolic. The changes in the T wave suggested occlusion of a coronary artery.

The patient was treated with rest in bed and theophylline for six weeks. He was active and had no complaints eighteen months later. Recently he had nocturnal dyspnea. He is now taking theophylline and is free from symptoms.

CASE 8.—A. S. W., aged 58, was first examined on May 11, 1933. He had had occlusion of a coronary artery six months before, and three months prior to examination he began to experience angina on effort. The heart was enlarged, and a systolic apical murmur was heard. The blood pressure measured 122 systolic, and 88 diastolic. The electrocardiogram showed bundle branch block.

The angina was relieved by theophylline, and the patient resumed his regular activities. He discontinued the use of theophylline about three months ago, and dyspnea returned. Theophylline was again given and relief was obtained.

CASE 9.—W. C., aged 58, was first examined on Jan. 31, 1933. There was a history of occlusion of a coronary artery three years before and of shortness of breath on exertion since that time. Occlusion of a coronary artery again occurred seven weeks prior to examination, and two mild attacks of pain were experienced since. Shortness of breath appeared on slight exertion. The heart was enlarged, and the cardiac sounds were of poor quality. The blood pressure measured 190 systolic and 120 diastolic. There were progressive changes in the T wave.

The patient took theophylline regularly for one year. He then discontinued the medication and experienced shortness of breath, but on resumption of the drug the symptoms disappeared. He now carries on his regular activities and has shortness of breath only on unusual exertion.

CASE 10.—B. P., aged 55, was first examined on Dec. 3, 1932. He gave a history of epigastric pain on exertion for six years, which was relieved by rest. Occlusion of a coronry artery occurred two weeks prior to consultation, and there was a severe attack of pain again on the day of examination. The heart was moderately enlarged, and changes in the quality of the cardiac tones were noted.

Rest in bed and theophylline were prescribed for six weeks; then gradual extension of activities was permitted. On a few occasions medication was discontinued, and dyspnea returned. He has taken theophylline regularly for more than one year.

CASE 11.—L. K., aged 58, was first examined on Aug. 1, 1933. He gave a history of fatigability five years before with hypertension. He experienced shortness of breath during the preceding five years and attacks of nocturnal dyspnea during the month prior to examination. Substernal oppression was also present. The heart was moderately enlarged. The blood pressure measured 114 systolic and 70 diastolic. Changes were observed in the T wave.

Theophylline was prescribed, and the same activities were permitted as were usual before examination. The patient felt much improved and had no recurrence of dyspnea until six weeks prior to the time of writing, after he had been without theophylline for a month. He took theophylline again, and the symptoms disappeared. This experience was recently repeated.

CASE 12.—Mrs. O. F. B., aged 72, was first examined on Aug. 2, 1930. Weakness, angina on effort and dyspnea had been present for the preceding eighteen months. During the greater part of this time she had been taking digitalis but did not think that she had improved. Just prior to consultation, the angina had been more severe. The heart was enlarged; the cardiac tones were muffled, and a systolic apical murmur was apparent. The blood pressure measured 140 systolic and 100 diastolic. The electrocardiogram showed bundle branch block.

The patient showed marked improvement after taking theophylline. Later, digitalis was prescribed, and the patient thought that it promoted the return of the pain. She was without discomfort for two years.

CASE 13.—Mrs. S. W., aged 71, was first examined on Aug. 14, 1930. There was a history of two attacks of retrosternal pain during the preceding three years. The present attack was typical of that observed in association with occlusion of a coronary artery. The cardiac sounds were muffled, and a systolic murmur was heard at the apex. The blood pressure measured 140 systolic and 88 diastolic. There were progressive changes in the T wave.

The patient took theophylline regularly for two years and was comfortable. Medication was stopped for two weeks, and retrosternal heaviness was noted. She began to take theophylline again, and the discomfort disappeared. She is very active, but she has observed that if she discontinues the use of the drug for a time the heaviness in the chest returns. She is now taking the theophylline regularly and is free from symptoms.

CASE 14.—Mrs. A. W. B., aged 70, was first examined on May 28, 1931. Occlusion of a coronary artery had occurred six weeks before, followed by congestive failure. She had had severe attacks of nocturnal dyspnea one week prior to examination. The patient had been in the hospital and was receiving digitalis. The heart was moderately enlarged; the cardiac tones were distant and muffled, and the rate was moderately increased. The blood pressure measured 115 systolic and 75 diastolic. Râles were heard in the base of each lung, and the liver was engorged. The electrocardiogram showed negative T waves in leads I and II, with elevation of the RT segment.

The patient was advised to continue treatment with rest in bed, and 1½ grains of theophylline ethylenediamine three times a day was added to the medication. She gradually improved. No further attacks of nocturnal dyspnea occurred. She has taken theophylline ethylenediamine regularly for several months. Now, three years later, she has no shortness of breath except on unusual exertion.

CASE 15.—W. H. McC., aged 63, was first examined on May 16, 1932. He had occlusion of a coronary artery in March 1932. He was in bed for four days and returned to work in six days. In a short time he began to have angina on effort. On May 10, 1932, a second attack of occlusion of

a coronary artery occurred. The pain was severe, and finally chloroform was administered for relief. The patient was short of breath. He remained in bed until May 15, 1932. The heart was slightly enlarged; the cardiac rate was 110; the tones were of poor quality, and there was a faint murmur. The blood pressure measured 105 systolic and 80 diastolic. Shortness of breath appeared on the slightest exertion. The patient was sent home to continue rest, and 1½ grains of theophylline ethylenediamine three times a day was prescribed. He was observed at intervals of from three to four months until October 1933. His condition was then satisfactory. There was no angina on effort or shortness of breath, except on rather vigorous exercise. The patient continued to take theophylline and was still well two years after the onset of the cardiac disability.

Case 16.—T. P. R., aged 60, was first examined on Feb. 19, 1925. Two weeks prior to examination he awakened with a feeling of fulness in the chest and difficulty in breathing. The feeling of heaviness lasted throughout the night. Since that experience he had had angina on effort and shortness of breath. The heart was slightly enlarged; the tones were distant, and no murmurs were heard. The blood pressure measured 90 systolic and 70 diastolic. The electrocardiogram showed suggestive changes in the T wave.

One and one-half grains of theophylline ethylenediamine three times a day was prescribed. The patient reported for a second examination two weeks later. No further angina was experienced. He returned again a year later and stated that he had been entirely free from cardiac symptoms. He attributed improvement to the use of theophylline.

Case 17.—C. D., aged 58, was first examined in October 1929, while suffering an attack of occlusion of a coronary artery. The occlusion apparently involved a large vessel. A possible attack of occlusion had occurred in 1926. He had had angina on effort for several months; the heart was slightly enlarged, and the tones were of poor quality. The blood pressure measured 140 systolic and 90 diastolic. Characteristic changes were observed in the electrocardiogram.

The patient received rest in bed for four weeks and was then permitted gradually to get on his feet. Three grains of theophylline ethylenediamine three times a day was prescribed. The dose was later reduced to 1½ grains three times a day. He has continued with this medication and is active and free from cardiac symptoms.

Comment.—The results in the aforementioned one hundred cases of paroxysmal dyspnea, angina on effort and occlusion of the coronary arteries are in general accord with what might be expected from the experimental study. It is to be noted that in a fairly large percentage favorable results were shown, and that in certain instances the change in the condition was striking. In the majority of the cases included in the group in which the results were questionable definite improvement was made, but when the variations in the course of the disease and other factors that might have a favorable influence on the disorder were excluded, the beneficial effects of the medication were doubtful. Finally, there were cases in which the results were definitely negative. Occasionally, an increase in the dose of theophylline brought about a distinct improvement in a patient for whom the results of the medication had been in doubt.

If one bears in mind the state of the coronary circulation generally presented in these conditions, it is not surprising that questionable results and failures are encountered. It is recognized from experimental and pathologic studies that much depends on the extent of the collateral circulation. It seems probable that the beneficial influence of theophylline is largely due to its action in promoting the development of this factor. If it is possible to develop and maintain an effective collateral circulation, theophylline is likely to be of value, but otherwise not. This may require time, and therefore the necessity of continuing the medication for a long period is evident. The importance of the continued use of the theophylline is well illustrated by certain cases already described.

We have been favorably impressed with the results of the use of theophylline in the treatment of acute occlusion of the coronary arteries. It should be recalled that in a number of cases cited the patients were first observed during or soon after occlusion of a coronary artery, the patients of the latter group usually coming for examination because of paroxysmal dyspnea, angina on effort or congestive failure. One of the 4 patients (case 3) who presented congestive failure had occlusion of a coronary artery ten days before admission to the hospital. While the response to theophylline may be prompt, even in cases in which the patient is not under observation for some time after the development of infarction, we believe that more lasting results are obtained when the medication is employed in the early stages of occlusion of a coronary artery.

CONCLUSION

It is important that measures be directed toward the restoration and maintenance of an efficient coronary circulation in the treatment of disease of the coronary arteries. The preparations of theophylline have a marked dilating action on the coronary vessels in the experimental animal, and clinical experience has demonstrated that they are valuable therapeutic agents in the treatment of disease of the coronary arteries, regardless of whether the cardiac disability is expressed by congestive failure, paroxysmal dyspnea, angina on effort or occlusion of the coronary arteries. Questionable results and failures are encountered, but this is to be expected in the more advanced forms of the disease. Theophylline should be prescribed as soon as the diagnosis of disease of the coronary arteries is established, and its administration should be continued for a long period, in order to insure the maximum benefit from the medication. It should be remembered, however, that this constitutes only one measure in the treatment and, except for experimental purposes, should not be employed to the exclusion of other established means of restoring the cardiac function.

CARBOHYDRATE INTOLERANCE AND INTESTINAL FLORA

I. A CLINICAL STUDY BASED ON SIXTY CASES

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Intestinal intolerance of carbohydrate with symptoms centering around marked meteorism is a rather common condition, the significance of which is often not appreciated. This symptom complex was first described by Schmidt and Strasburger [1] in 1901 in Germany and by Herter [2] in 1907 in this country. In the recent English medical literature the only publications on this subject have been by Kendall [3] and Hurst and Knott.[4] Textbooks usually ignore this condition.

In our gastro-intestinal clinic, during the past five years, in 9 per cent of the cases the major diagnosis was intestinal intolerance of carbohydrate. This figure exaggerates the frequency of the condition among patients with conditions related to the digestive tract, as a disproportionately large number of patients with obscure conditions are referred to this clinic for diagnosis, but it indicates that this syndrome is fairly common.

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Read at the thirty-sixth annual meeting of the American Gastro-Enterological Association, Washington, D. C., May 8, 1933, and before the General Medicine Section of the California Medical Association at the sixty-third annual session, Riverside, May 3, 1934.

1. Schmidt, A., and Strasburger, J.: Experimentelle und klinische Untersuchungen über Functionsprüfung des Darmes: VI. Ueber die intestinale Gährungsdyspepsie der Erwachsenen, Deutsches Arch. f. klin. Med. **69**:570, 1901.

2. Herter, C. A.: The Influence of Food and of Epithelial Atrophy on the Manifestations of Saccharo-Butyric Intestinal Putrefaction, J. A. M. A. **49**:1965 (Dec. 14); 2077 (Dec. 21) 1907.

3. Kendall, A. I.: Intestinal Intolerance for Carbohydrate, Associated with Overgrowth of Gas Bacillus (Bacillus Welchii), J. A. M. A. **86**:737 (March 11) 1926.

4. Hurst, A. F., and Knott, F. A.: Intestinal Carbohydrate Dyspepsia, Quart. J. Med. **24**:171, 1931.

CLINICAL PICTURE

From a survey of fifty consecutive cases we find that this disease occurs in females four times as often as it does in males. About 60 per cent of our patients at the time of observation were between the ages of 30 and 50 years. Few were younger. On the other hand, the onset of symptoms in two thirds of the cases occurred between the ages of 20 and 40 years. The shortest duration of symptoms was six

TABLE 1.—*Frequency of Gastro-Intestinal Symptoms in Fifty Cases of Intestinal Intolerance of Carbohydrate*

Symptoms	Percentage
Meteorism	100
Abdominal pain	84
Nocturnal distress	70
Excessive flatus	74
Belching	76
Constipation	82
Diarrhea (periodic or chronic)	28
Mucus in stools	30
Periodic digestive upsets	60
Conscious intolerance of carbohydrate	66

TABLE 2.—*Incidence of Systemic Manifestations in Fifty Cases of Intestinal Intolerance of Carbohydrate*

Systemic Manifestations	Percentage
Asthenia	98
Nervousness	88
Vasomotor instability	80
Blood pressure:	
Hypotension	38
Normal	58
Hypertension	4
Gastric acidity:	
Achlorhydria	14
Hypochlorhydria	52
Normal	28
Hyperchlorhydria	6
Anemia	40
Albuminuria	6
Chronic choroidoretinitis	24
Cardiac consciousness	52

weeks; the longest, twenty-three years; the average was more than four years.

The incidence of the various findings in our cases is shown in tables 1 and 2. Flatulence was marked in all the patients. Abdominal distress ranged from a sense of pressure to pain of a dull or colicky nature and was present in four of five cases. Flatus in excessive amounts was almost as common and, as a rule, was relatively odorless. Belching, another frequent symptom, was very annoying in some cases. Waking during the night due to abdominal distress, when present, is almost pathognomonic of this condition. It occurred most frequently between midnight and 3 o'clock in the morning. Patients are usually able to

control their nocturnal distress by walking around, massaging the abdomen or taking a warm drink and, finally, after passing some gas, fall asleep again.

Many patients suspect a relationship between the ingestion of certain carbohydrate foods and the exacerbation of symptoms, while from others this information is elicited only by careful questioning. The latter is not surprising, because starches in some form are part of every meal. Most frequently the offending article of food is the potato, but many patients also have a great deal of trouble with milk. Dried beans, peas and lentils are rarely mentioned by patients, because most of them have learned long ago to avoid them altogether. Three patients in this series named candy and sugar as the worst offenders. The intensity of symptoms is not uniform but rather is characterized by intermittent exacerbations which, in more than half of the cases, assume the proportions of an attack lasting for several days.

Constipation was present in most cases. Among the more severe cases periodic attacks of diarrhea or habitual looseness of the bowel was the rule. In about half of the patients having periodic diarrhea the condition could be classified as mucous colitis. Fifteen per cent of our patients had increased amounts of mucus in their stools without diarrhea. The feces in this condition are normal or light in color, usually acid to litmus and often show many bubbles of gas. Microscopic examination after the addition of compound solution of iodine U. S. P. reveals in most cases blue-staining granules of starch, but these are also frequently found in normal specimens. On the whole, examinations of the stool yield no information of great diagnostic value. The presence of much mucus has an unfavorable prognostic significance.

Two thirds of all the patients had diminution or absence of free hydrochloric acid in the stomach. Roentgenologic studies of the colon were carried out in thirty patients but showed no consistent abnormalities. In many cases dilatation of the colon was observed. Other patients had minor abnormalities such as ptosis, spasticity or redundancy. In a number of patients tenderness along the course of the large bowel was noticed.

Turning to symptoms outside of the digestive tract, asthenia and nervousness were prominent, in point of both frequency and severity. Vasomotor instability in varying degrees, sometimes with dizziness, sometimes with severe frequent headaches, was also an important characteristic in most cases. In addition, five patients suffered from a mild form of Raynaud's disease.

More than one half of the patients complained of palpitation and extrasystoles. The blood pressure was found to be normal in a majority and low in a considerable proportion of cases. Even mild hypertension was rare. About one fourth of our patients were found to have chronic

choroidoretinitis, sometimes with impairment of sight. Anemia with less than 80 per cent hemoglobin and a red blood cell count under 4,200,000 was present in 40 per cent of our cases.

The urine of almost all the patients was normal. An important exception was presented in a group of instances collected by one of us (S. J. S.) because of pronounced intolerance to starches combined with multiple toxic symptoms. Albuminuria was invariably among the latter. Occasionally hematuria and cylindruria were also present, without other evidence of nephritis. The clinical features of these cases are summarized separately in tables 3 and 4.

TABLE 3.—*Frequency of Gastro-Intestinal Symptoms in Ten Cases of Intestinal Intolerance of Carbohydrate with Toxic Signs*

Symptoms	Percentage
Meteorism	100
Abdominal pain	100
Nocturnal distress	50
Excessive flatus	100
Constipation	...
Chronic diarrhea	100
Mucus in stools	50
Periodic digestive upsets	80
Conscious intolerance of carbohydrate	100

TABLE 4.—*Incidence of Systemic Manifestations in Ten Cases of Intestinal Intolerance of Carbohydrate with Toxic Signs*

Systemic Manifestations	Percentage
Asthenia	100
Nervousness	100
Vasomotor instability	100
Blood pressure:	
Hypotension	...
Normal	67
Hypertension	33
Anemia	90
Urinary findings:	
Albuminuria	100
Hematuria	20
Cylindruria	20
Chronic choroidoretinitis	40
Extrasystoles	100

Persons suffering from intestinal intolerance of carbohydrate are, as a rule, very unhappy and often become incapacitated, especially during the periodic exacerbations to which they are subject. One is struck by the faithfulness with which these patients, most of whom have undergone many types of unsuccessful therapy, follow rigid dietary restrictions and by the great length to which they go in order to secure competent medical advice.

ETIOLOGY AND PATHOGENESIS OF SYMPTOMS

1. *Local Gastro-Intestinal Manifestations.*—The flatulence in intestinal intolerance of carbohydrate is real, as is shown by the prominence

which the passage of large amounts of flatus occupies among the complaints. This was substantiated by the finding of abdominal distention and palpable gas, especially in the region of the cecum and of the splenic flexure. Having established an undue accumulation of gas, one must decide whether it is caused by excessive production of gas in the intestine or by interference with absorption of normally formed gases into the blood preparatory to their elimination through the lungs.

At the beginning of this investigation, on the basis of reports in the literature, a positive outcome of fermentation tests [5] was accepted as proof of excessive production of gas in the colon. Later a critical investigation into the significance of these tests forced us to the conclusion that they are worthless, at least from the clinical standpoint. This opinion is supported by the experience of other workers [6] that stormy fermentation can be produced by stools of persons without flatulence.

There are several possible causes of increased intestinal fermentation to be considered. Herter [7] and, later, Kendall [8] suggested as a cause changes in the intestinal flora, chiefly an overgrowth of Clostridium Welchii, made possible by reduction in the activity or number of lactic acid organisms. Kendall further strengthened this opinion by showing that dietary measures restraining the activity of these microbes are of therapeutic value in intolerance of carbohydrate. Similarly, Simonds [9] and Torrey [10] see in stormy fermentation proof of a predominance of the Welch organism in the stool.

In conflict with this view are the results of our own quantitative studies of Cl. Welchii, which demonstrated that even extreme degrees of stormy fermentation may occur with only small numbers of this micro-organism in the stools. Moreover, contrary to the hypothesis of Herter, no consistent correlation could be made between numbers of the Welch bacillus in the fecal flora and intolerance of carbohydrate. Some

5. Details of the bacteriologic studies are given in the second paper of this series.

6. MacNeal, W. J.; Latzer, L. L., and Kerr, J. E.: The Fecal Bacteria of Healthy Men, J. Infect. Dis. **6**:571, 1909. Hewes, H. F., and Kendall, A. I.: The Gas Bacillus as an Agent of Intestinal Fermentation and Diarrhea, Boston M. & S. J. **166**:75, 1912. Schmidt and Strasburger.[1]

7. Herter, C. A.: The Common Bacterial Infections of the Digestive Tract and the Intoxications Arising from Them, New York, The Macmillan Company, 1907, p. 291.

8. Kendall, A. I.: Hypotension, Illinois M. J. **56**:404, 1929; footnote 3.

9. Simonds, J. P.: Studies in Bacillus Welchii with Special Reference to Classification and to Its Relation to Diarrhea, Monogr. 5, Rockefeller Institute for Medical Research, 1915.

10. Torrey, J. C.: The Fecal Flora of Typhoid Fever and Its Reaction to Various Diets, J. Infect. Dis. **16**:72, 1915.

patients with this condition had very large numbers of the Welch organism, while others had but a few. The most consistent overgrowth of Cl. Welchii was found in a small group of patients with hypochromic anemia and achlorhydria. The same wide and unaccountable variations were found in the number of aciduric organisms. Similarly, no definite relationship could be found between clinical features in different cases and the amount of putrefaction or the presence of various types of streptococci and of hemolytic Bacillus coli in the stools. In practically all the cases the flora was moderately proteolytic.

A second possibility which could account for the increased production of gas is the upward extension of the colonic flora into regions of the ileum and jejunum, where absorption of carbohydrates normally takes place in almost complete absence of bacteria. The opportunities for greatly increased fermentation under such conditions are obvious, even in the absence of qualitative changes in the bacterial flora.

The fecal flora is normally restrained from growing above the lower ileum by the hydrogen ion concentration of the small intestine, which is dependent on normal gastric secretory function.[11] In achlorhydria, Arnold and Brody,[12] Knott [13] and others found the colonic flora extending into the jejunum and even into the duodenum. Porges and Essen [14] reported in some cases of fermentative diarrhea infestation of the ileum by starch-fermenting bacteria. In addition, Herter,[15] Bogendörfer [16] and Kendall and Schmitt [17] demonstrated an extension of Cl. Welchii into the small intestine of patients with absence or diminution of gastric acidity. A better understanding of the mechanism of such a bacterial invasion of the small intestine from below can be gained from Nechoroschew's [18] description of cyclic variations in the

11. Arnold, L., and Brody, L.: The Gastro-Duodenal Bactericidal Mechanism, Am. J. Hyg. **6**:672, 1926.

12. Arnold, L., and Brody, L.: Bacterial Flora and Hydrogen Ion Concentration of Duodenum, J. Infect. Dis. **38**:249, 1926.

13. Knott, K. A.: Addison's Anemia and Subacute Combined Degeneration of the Cord; Rôle of Achlorhydria and Intestinal Infection, Guy's Hosp. Rep. **77**:1, 1927.

14. Porges, O., and Essen, H.: Ueber die Pathogenese und Therapie der sogenannten dyspeptischen Diarrhöen, Ztschr. f. klin. Med. **109**:12, 1928.

15. Herter, C. A.: On Bacterial Processes in the Intestinal Tract in Some Cases of Advanced Anemia, with Especial Reference to Infection with B. Aerogenes Capsulatus (B. Welchii), J. Biol. Chem. **2**:1, 1906.

16. Bogendörfer, L.: Ueber die Flora des menschlichen Dünndarmes, Deutsches Arch. f. klin. Med. **140**:257, 1922.

17. Kendall, A. I., and Schmitt, F. O.: Physiologic Action of Certain Cultures of the Gas Bacillus, J. Infect. Dis. **39**:250, 1926.

18. Nechoroschew, N. P.: Periodische Tätigkeit des Verdauungkanals und Darmflora, Ztschr. f. d. ges. exper. Med. **66**:10, 1929.

duodenal flora of dogs. He found that during periods of rest the duodenal flora gradually increased, to reach its maximum just before a period of activity (as shown by balloons placed in the intestine). During periods of activity acid waves from the stomach forced the flora to retreat and sterilized the duodenum. Since the majority of our patients were found to have a decrease or absence of hydrochloric acid in the stomach, and since Herter [2] and Kendall [3] also reported the frequent occurrence of hypochlorhydria in intolerance of carbohydrate, conditions in this syndrome must be favorable for an invasion of the small intestine by colonic organisms.

Of great interest in this connection is the work of Arnold,[19] indicating that alterations in the equilibrium of the autonomic nervous system, especially any changes in the heat-regulatory mechanism, may inhibit the normal bactericidal power of the small intestine, allowing the fecal flora to ascend into the upper part of the alimentary tract. The phenomena of vasomotor instability in 80 per cent of our patients, which has already been mentioned and which was also noticed by Herter,[2] may in this light constitute an important factor in facilitating an upward extension of the intestinal flora. Of further significance is the fact that potatoes, beans and root vegetables, as a rule, are more troublesome to patients than bread and macaroni. In the former the starch is enclosed in cellulose envelops of varying thickness [20] and therefore is not readily absorbed, reaching the lower part of the ileum. In the latter foodstuffs the starch is freed from its cellulose covering by milling and is absorbed higher in the small intestine. It may seem surprising that milled starches and sugar should cause any intestinal fermentation at all, a fact also noticed by Herter [2] and Kendall.[3] However, there is evidence that white bread and saccharose, if taken in large amounts, may reach the cecum.[21] Also, the fecal flora can, in some cases, extend as high up as the duodenum. The marked intolerance of our patients to lactose, which is absorbed so slowly that when fed in large amounts it may even be detected in the stools,[22] is probably to be explained on the same basis.

One of our cases illustrates well what may happen when a fecal flora establishes itself in the ileum. A woman, aged 30, who four years

19. Arnold, L.: The Passage of Living Bacteria Through the Wall of the Intestine and the Influence of Diet and Climate upon Intestinal Autoinfection, Am. J. Hyg. **8**:604, 1928.

20. Strauss, L.: Verdauung von Stärke aus geschlossenen Zellen, Arch. f. Verdauungskr. **41**:11, 1927.

21. Torrey, J. C.: The Regulation of the Intestinal Flora of Dogs Through Diet, J. M. Research **39**:415, 1918.

22. Hull, T. G., and Rettger, L.: The Influence of Milk and Carbohydrate Feeding on the Character of the Intestinal Flora, J. Bact. **2**:47, 1917.

previously had undergone removal of the colon for multiple polyposis, entered the University of California Hospital complaining of symptoms related to a severe degree of intolerance for carbohydrates. On investigation, the lower part of the ileum was found to have assumed some of the characteristics of the colon. Part of the time the patient passed soft but formed stools through the ileostomy opening, showing that considerable dehydration of the intestinal contents took place. Haustral markings were demonstrable in the ileum at the beginning of a barium sulphate enema but were later obliterated by greater filling of the bowel. Finally an atypical fecal flora with predominance of yeasts, streptococci and Cl. Welchii was found in the stools. The passage of much mucus, the absence of free hydrochloric acid in the gastric contents during fasting and failure to obtain relief from treatment were also important features of this case.

The third possible cause for increased fermentation lies in the penetration of abnormally large amounts of sugar or starch into the colon. Rapid passage of chyme through the small intestine could produce this. Porges and Essen [14] observed increased motility of the small intestine roentgenologically in a certain proportion of persons suffering from "fermentative diarrhea." In one of their cases barium sulphate appeared in the rectum two hours after it was given by mouth. Moreover, these observers were able to bring about a disappearance of undigested starch from the stools of these patients by the administration of opium. At least one of our patients also had intestinal hypermotility, as charcoal used to appear in his stools about six hours after ingestion. Porges and Essen quote an ingenious explanation of the origin of fermentative diarrhea from Schmidt and von Noorden's book [23] to the effect that products of fermentation accelerate the emptying of an abnormally sensitive colon and reflexly bring about hypermotility of the small intestine, which sends increased amounts of undigested starch into the colon, thereby still further increasing fermentation. On the other hand, increased motility of the small intestine might be due directly to the formation of butyric and other irritating acids by fermentation within its lumen.

Carbohydrate foods, especially starch in unruptured vegetable cells, when eaten in excess, might prove to be beyond a person's capacity to digest and to absorb during passage through the small intestine. A suggestive case of this nature came to our attention when a woman suffering from intolerance of carbohydrate consulted us about her son, aged 10, whom she had been "stuffing with starchy foods" in

23. Schmidt, A., and von Noorden, C. H.: Darmkrankheiten, Munich, J. F. Bergmann, 1921; quoted from Herter.[15]

an attempt to increase his weight. The child had most of the intestinal but none of the systemic manifestations of intolerance for carbohydrates. He was cured by merely being put on a reasonable diet.

Hurst and Knott [4] attributed excessive fermentation in patients with this syndrome to failure of digestion of unruptured granules of starch in the small intestine due to an insufficiency of ferments caused by previous enteritis. Their explanation involves the combination of an insufficiency of a hypothetic amylolytic ferment in the succus entericus with continued activity of an as yet undemonstrated diastase secreted in the cecum. In addition, the authors claimed that intestinal intolerance of carbohydrate does not occur in the presence of achlorhydria, because in the absence of hydrochloric acid digestion of starches is completed by the unchecked action of salivary ptyalin in addition to that of pancreatic amylopsin. The first part of this theory appears to us speculative,[23a] and the second part is contradicted by our experience with seven patients who had intolerance for carbohydrates in the presence of achlorhydria. Moreover, this explanation does not account for the occasional patients who have less tolerance for sugar than for starches. Finally, in contrast to Hurst and Knott, we were able to elicit a history of previous infection in the small bowel (mainly typhoid fever) in only five of our cases. Faulty digestion or poor absorption of carbohydrates in the small intestine without abnormal motility theoretically may account for the fact that excessive amounts of starch reach the colon, but so far no cases have come to our attention in which there was evidence in favor of either of these conditions.

There are persons who have no flatulence and yet consistently pass stools which contain enormous numbers of Cl. Welchii and other fermentative organisms. Since some of these persons also have achlorhydria and therefore conditions favorable for an upward extension of the fecal flora and yet deny bloating, one is compelled to search for factors other than mere increase in intestinal fermentation in order to explain the symptom complex of intolerance for carbohydrates. Such a factor one finds in interference with the absorption of gases from the intestinal lumen. In discussing the importance of various conditions contributing to the production of flatulence, Alvarez [24] writes: "Even

23a. Since this was written, Dr. W. H. Owles, at the Thorndike Memorial Laboratory in Boston, found by direct examination of normal persons "a completely insignificant production of diastase in the small intestine" which he was "unable to increase to a significant value by any means (food by mouth, locally, etc.)." Dr. Owles also investigated the case of one patient with intestinal intolerance to carbohydrate who had "high normal pancreatic diastase." (Personal communication to the authors.)

24. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, Paul B. Hoeber, Inc., 1928, chap. 26, p. 347.

when fermentation is active, other factors must enter in before the patient can be annoyed by flatulence, because normally so much of the gas is promptly taken up by the blood and excreted by the lungs." Then he proceeds to enumerate several factors favoring flatulence and assigns an important place to interference with the intestinal absorption of gases and to changes in the intestinal circulation. Schoen,[25] who did some excellent experimental work on the diffusion and resorption of intestinal gases under physiologic and pathologic conditions, went even further, stating that interference with the resorption of gases is a more important cause of flatulence than the excessive production of gases.

Schoen considered a loss of tonus by the intestinal musculature the most important factor interfering with the absorption of gases and supported his view by showing that pilocarpine increases and atropine markedly diminishes the resorption of gas from the intestine. These findings may have an important bearing on our clinical syndrome, because asthenia with weakness of the abdominal wall and consequent low intra-abdominal pressure was a constant finding in our patients. Schmidt and Strasburger,[1] Herter [2] and Kendall [3] also commented on the asthenia and low physical endurance common to their patients with intolerance of carbohydrate. Excessive distention of the intestine by gas and the paralyzing effects of some intestinal toxins, especially those of the amine group, on the smooth musculature of the bowel were considered by Schoen additional factors interfering with the intestinal absorption of gases. We have already pointed out that excessive gaseous distention is a constant complaint among our patients. The formation of toxic substances in the bowel is also possible and will be considered later.

Schoen suggested that another factor decreasing the absorption of gases may be interference with the intestinal circulation by excessive distention. Van Zwalenburg [26] and Dragstedt, Lang and Millet [27] furnished quantitative data on this subject. The former author showed that an intra-intestinal pressure of 30 mm. of mercury begins to slow the blood flow of the intestine, while a pressure of 130 mm. stops it entirely. The latter investigators found that the duodenum, jejunum and ileum were sensitive to increases in intestinal pressure in that order; that a pressure of 20 mm. of mercury had a noticeable effect, and that an intrajejunal pressure of 80 mm. of mercury reduced the

25. Schoen, R.: Experimentelle Untersuchungen über den Meteorismus, Deutsches Arch. f. klin. Med. **147**:224, 1925; **148**:86, 1925.

26. Van Zwalenburg, C.: Strangulation Resulting from Distention of Hollow Viscera, Am. J. Surg. **46**:780, 1907.

27. Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: The Relative Effects of Distention on Different Portions of the Intestine, Arch. Surg. **18**:2257 (June) 1929.

jejunal blood flow by about 60 per cent. Vasomotor relaxation due to nervousness or to the action of toxins on the smooth muscle fibers of the blood vessels may be another contributing cause. Alvarez stated that "the flatulence of nervous persons might be due at least in part to upsets in the gas exchange of the bowel, associated with an internal blushing and blanching similar to that which takes place so commonly in the skin." As shown in tables 2 and 4, almost all our patients were nervous, and, in addition, a great majority had vasomotor instability. Similar findings for this syndrome were reported by other medical writers.

What gas or gases are responsible for flatulence in intestinal fermentation? Six gases commonly present in the intestine must be considered.[28] Oxygen is usually found only in amounts under 1 per cent and is readily utilized by bacteria and absorbed into the blood. The nitrogen content of the intestinal gas varies from 10 to 60 per cent. This gas comes from the air, and there is practically no absorption of it from the intestine even under most favorable conditions. Methane may be present in the intestine to the extent of 50 per cent. Its formation is favored by a diet of legumes and, to a lesser degree, by a diet rich in meat. Little of this gas is found in persons on a milk diet. Hardly any methane is produced by the fermentation of starch and sugars, and only minimal amounts of it are resorbed, even by the normal intestine. It is, therefore, clear that the decreased absorption of gases would not appreciably increase the amount of oxygen, nitrogen or methane in the bowel. Hydrogen sulphide probably also plays little or no part in most cases of intestinal intolerance for carbohydrates, as shown by the relatively odorless nature of the flatus.

There is usually less than 5 per cent of uncombined hydrogen in the intestinal gas of a normal person on a mixed diet, but this proportion may rise to as high as 55 per cent in persons on a milk diet. Since from two thirds to three fourths of gas arising from the fermentation of carbohydrates is hydrogen, and since even normally it is absorbed from the intestine to only a moderate degree, the importance of this gas for the production of flatulence in patients with increased intestinal fermentation is at once apparent.

Carbon dioxide is represented in the flatus of normal persons to the extent of from 5 to 40 per cent. From one fourth to one third of the gas evolved by the fermentation of carbohydrate is carbon dioxide.

28. Ruge, E.: Beiträge zur Kenntnis der Darmgase, Chem. Centralbl.-Bl. **7**:347 and 353, 1862. Fries, J. A.: Intestinal Gases of Man, Am. J. Physiol. **16**:468, 1906. Bokai, A.: Experimentelle Beiträge zur Kenntnis der Darmbewegungen, Arch. f. exper. Path. u. Pharmakol. **23**:207, 1887. Simonds.[9] Alvarez.[24] Schoen.[25]

Since this gas is resorbed three times as rapidly as the next most absorbable gas, any interference with the resorption of gases from the intestine is particularly apt to cause flatulence due to the accumulation of carbon dioxide. In addition, carbon dioxide, in contrast to oxygen, nitrogen and hydrogen, has been shown to have also a chemically irritating action on the bowel.

In concluding this survey of possible causes of flatulence in intestinal intolerance of carbohydrate, the conclusion seems inescapable that in every patient several factors favoring increased fermentation and interfering with resorption are operative in bringing about the accumulation of gases in the bowel, and that in various cases different factors may be in the foreground. The relative importance of excessive fermentation and decreased absorption of gases in the production of meteorism in individual cases of this condition might be learned from the relative proportions of hydrogen and carbon dioxide in the flatus. To date there are no analyses of intestinal gases in this condition on record.

Constipation, when present, may be of contributory significance in the genesis of meteorism, because stagnation of intestinal contents is recognized as favoring flatulence.[13] On the other hand, according to Zinsser,[29] the abnormal splitting of carbohydrates, with the production of butyric and other organic acids, in itself results in hyperacidity which may cause stasis of the bowel. In fact, constipation is a common symptom in patients with intolerance of carbohydrate. In cases in which organic acids are produced in larger amounts diarrhea in periodic attacks appears and finally may become chronic in severe cases. Bokai [30] substantiated this experimentally by injecting organic acids formed by the fermentation of sugars into the bowel and producing diarrhea. The irritating action of carbon dioxide may contribute both to early constipation and to late diarrhea.

The abdominal distress and waking at night are probably due mainly to gaseous distention, because the passage of flatus is always accompanied by at least partial relief. Intestinal spasm from irritating products of fermentation may also be a source of pain in the abdomen.

Increased amounts of mucus, which is present in the stools in the more severe cases, confirm the existence of chronic intestinal irritation. Simonds [9] and especially Sittler [31] consider the mucous covering of the intestine a favorite habitat of Cl. Welchii, even in normal persons. We also noticed that in patients with much mucus in the stools the condition

29. Zinsser, H.: A Text Book of Bacteriology, New York, D. Appleton & Company, 1923, p. 227.

30. Bokai, A.: Experimentelle Beiträge zur Kenntnis der Darmbewegungen, Arch. f. exper. Path. u. Pharmakol. **24**:151, 1887.

31. Sittler, P.: Die wichtigsten Bakterientypen der Darmflora beim Säugling, Würzburg, C. Kabitzsch, 1909; cited by Kendall.[6]

was often refractory to treatment. Porges and Essen [14] made similar observations in cases of fermentative diarrhea. It is possible that an excess of mucus offers a specially good soil for spore-forming, carbohydrate-fermenting anaerobes, or that it in some way protects these organisms against therapeutic measures.

Belching may be a disagreeable feature, especially to the fastidious patient. In some cases it is doubtless due to the swallowing of air in an effort to relieve the feeling of distention which the patient attributes to the presence of gas in the stomach. On the other hand, there are patients, particularly those having single large eructations spaced at considerable intervals, in whom gases formed probably in the upper part of the small intestine collect in the stomach. This can be determined by placing a cork between the teeth to prevent the swallowing of air or by analysis of the eructated gas.

2. *Systemic Manifestations.*—Among the complaints of patients with intestinal intolerance of carbohydrate is a train of symptoms consisting of marked asthenia, fatigability, nervousness and vasomotor instability. To these are often added frequent severe headaches, hypotension and hypochlorhydria. Patients in the group with toxic symptoms also emphasize mental symptoms variously described as "feeling fagged," "unable to think clearly," etc. The origin of these symptoms, which collectively represent a state typical for patients with intolerance of carbohydrate, is not entirely clear. However, it probably will not be far from the truth to interpret them as the constitutional background of persons who fall victims to this condition. An overlay created by several years of chronic distress and possibly, in a small number of cases, also by the absorption of toxic substances from the intestine, intensifies these constitutional characteristics.

The enumerated symptoms are not due to constipation, because practically all "constipated" patients in this series kept their bowels open by daily catharsis, while in the more severe cases there were at least two or three spontaneous loose stools a day. An analysis of coexisting diseases in these patients occasionally permitted us to account for some general symptoms on the basis of focal infection, postmenopausal ovarian insufficiency, arteriosclerosis and other conditions, but was never sufficient to explain the whole clinical picture.

Of great theoretical and practical importance among the systemic manifestations of this syndrome are anemia, albuminuria and chronic choroidoretinitis, because we feel justified in ascribing them to the absorption of toxic substances from the intestine. Anemia was present in 40 per cent of the fifty consecutive cases. Anemia was more frequent and more severe among patients selected for the presence of toxic symptoms. Of ten cases in this group, in one the blood was normal; in

another case the erythrocytes numbered 4,240,000, and in eight cases the red blood cells ranged between 2,710,000 and 3,860,000. After these patients were put on a diet low in starches their blood, without exception, showed a gradual rise of erythrocytes to a normal level of at least 4,500,000 and, in most cases, even higher. Anemia in cases of intolerance for carbohydrates had been previously noticed by Schmidt and Strasburger [1] and was emphasized by Herter.[15]

An extensive literature linking different types of anemia with the intestinal absorption of toxic substances is ably reviewed by Moench, Kahn and Torrey [32] and by van der Reis.[33] However, these reviews do not mention the recently much discussed hypochromic anemia, which in many respects bears a striking resemblance to intestinal intolerance of carbohydrate. To cite fragments from a paper by Dameshek [34] on this subject, "The disease is almost wholly confined to women; the chief complaint is weakness or easy fatigue; other important complaints are belching of gas and a sense of fulness in the epigastrium; diarrhea is occasionally present, but constipation is more likely; a history of a burning or sore tongue is often present; nervousness is almost invariably present; younger women have the atrophied, wrinkled skin seen only in the aged." To this we can add, from our own observations on a small number of patients, the presence of large numbers of Cl. Welchii in the stools. To make this resemblance even closer, Herter [35] also commented on premature senility of the skin and muscles and made much of the soreness of the tongue in his cases of intolerance for carbohydrates. We also met with the latter symptom in several of our cases, and in one of these it was the main complaint. In this patient the tongue improved following the strict limitation of carbohydrates in the diet.

Albuminuria was rare in our unselected series but was found in all cases of the toxic group. Remarkable, again, was the disappearance of albumin from the urine of all but one patient following the dietetic regimen. In the single exception albuminuria was diminished but did not disappear altogether. In another case albumin, red blood cells and casts had been observed in the urine for one year, with normal results of tests of renal function. When this patient rigidly restricted the intake of starches, the abnormal constituents of the urine disappeared but reappeared again on several attempts to raise the allowance of starches.

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32. Moench, L. M.; Kahn, M. C., and Torrey, J. C.: Analysis of the Fecal Flora in Thirty-Three Cases of Pernicious Anemia, J. Infect. Dis. **37**:161, 1925.

33. van der Reis, V.: Die Darmbakterien des Erwachsenen und ihre klinische Bedeutung, Ergebn. d. inn. Med. u. Kinderh. **27**:77, 1925.

34. Dameshek, W.: Primary Hypochromic Anemia: II. Clinical Features, J. A. M. A. **100**:540 (Feb. 25) 1933.

35. Footnote 7, p. 299. Footnote 2.

Since these patients were not suffering from protein undernutrition, the curative effects of a low carbohydrate diet seem to indicate that the anemia and albuminuria in intestinal intolerance of carbohydrate are in some way associated with the elaboration of toxic substances in the intestine incident to increased fermentation.

Chronic choroidoretinitis was found frequently in our patients, especially among those with other toxic symptoms. It probably is a manifestation of the same intoxication which we suspect of affecting the blood and the kidneys. It is difficult to judge the results of treatment by its effect on choroidoretinitis, because this condition is chronic and in healing leaves scars.

To these signs of systemic intoxication may be added, with certain reservations, extrasystoles, which were also particularly frequent in the group with toxic symptoms. However, the frequency with which extrasystoles and other forms of cardiac consciousness were found, even in patients without toxic symptoms, makes one look for some other explanation. Such an explanation can be seen in excessive abdominal distention, which may embarrass the heart mechanically by pushing the diaphragm up or, as claimed by Fundner,[36] may affect the cardiac rhythm reflexly. This, however, does not exclude toxic irritability of the myocardium.

INTESTINAL TOXINS

Substances which may be formed in the intestine that are capable of exerting a harmful local or systemic influence can be divided into two classes: nonspecific toxic substances and bacterial toxins. Among the first are a number of organic acids arising during the fermentation of carbohydrates, which may cause local irritation of sufficient magnitude to produce diarrhea in man.[9] The most important of these is butyric acid, which is produced in proportions of between 5:1 and 12:1 to the acid next in importance, lactic acid. Weak solutions of butyric acid, when introduced into the colon, produce hyperemia and violent contractions of the colon to a more marked degree than similar solutions of lactic acid.[30] Other organic acids formed in the bowel through fermentation are valerianic, propionic, formic and acetic acid, but they are quantitatively unimportant.

Zinsser [29] states that the abnormal splitting of carbohydrates may result in stasis of the bowel, with secondary putrefaction and the formation of histamine and other toxic amines. These toxic substances may act locally and, as advocated by Schoen,[25] exert a paralyzing action on the smooth muscle of the intestine and blood vessels, thereby inter-

36. Fundner: Ueber den Einfluss intraabdominaler Drucksteigerung und des Füllungszustandes des Magens auf den Blutdruck, Deutsches med. Wchnschr. **39**: 646, 1913.

fering with the resorption of gases. Or they may become absorbed into the circulation and, if not completely detoxified in the liver, exert a widespread deleterious action. An important objection to such an action of histamine is that, as shown by Mellanby,[37] this compound is readily destroyed by bacterial action. In addition, there are reasons to think that histamine is never produced in the presence of carbohydrates.[38] In view of this, it is difficult to consider histamine responsible for symptoms in a condition that is particularly aggravated by the intake of carbohydrates which stay longer in the intestine.

Several investigators,[39] on the basis of their experiments, came to the conclusion that the intestinal mucosa, at least at some levels, is permeable to bacterial toxins. In addition, Cannon [40] has shown that the absorption of toxic substances from the intestine is favored by raising the intestinal pressure, and that this is independent of the increase in the mucosal surface. He further states that in gaseous distention both factors may be concerned in the production of toxemias. The bearing of these observations on the conditions existing in our patients is obvious.

Among bacterial toxins, those produced by Cl. Welchii have received a great deal of attention. The idea of connecting an overgrowth of this vigorous carbohydrate-fermenting organism with toxic manifestations has its attractions. Through the efforts of a number of workers, notably, Passini,[41] Bull and Pritchett,[42] Henry,[43] Katzumi,[44] Moench, Kahn and Torrey [32] and Kendall and Schmitt,[17] Cl. welchii has been shown to elaborate, under certain conditions, several distinct toxic substances: a hematoxin which could account for anemia, a myotoxin which might be responsible for asthenia and extrasystoles, a neurotropic toxin causing symptoms referable to the nervous system and a histamine-like

37. Mellanby, E.: An Experimental Investigation on Diarrhea and Vomiting of Children, Quart. J. Med. **9**:165, 1915.

38. Alvarez, W. C.: Autointoxication, Physiol. Rev. **4**:352, 1924.

39. Kahn, M. C., and Torrey, J. C.: The Possible Relationship Between Absorption of B. Welchii Toxin and Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **24**:413, 1926. Herter.[2] Moench, Kahn and Torrey.[32]

40. Cannon, T. R.: The Effects of Diet on the Intestinal Flora, J. Infect. Dis. **29**:369, 1921.

41. Passini, F.: Ueber Giftstoffe in den Kulturen des Gasphlegmonbazillus, Wien. klin. Wchnschr. **18**:921, 1905.

42. Bull, C. G., and Pritchett, I. W.: Toxin and Antitoxin of and Protective Inoculation Against Bacillus Welchii, J. Exper. Med. **26**:119, 1927.

43. Henry, H.: On the Composition of B. Welchii Toxin, J. Path. & Bact. **26**:497, 1923.

44. Katzumi, Kajima: Beiträge zur Erforschung der Rauschbranderreger: I. Die Toxinbildung des Typus Foth und die toxikologischen, immunisatorischen und biochemischen Eigenschaften des Toxins, Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**:170, 1923.

substance to which hypotension and other vascular phenomena might be ascribed. Another intriguing aspect of this problem, brought out by Passini,[41] Bull and Pritchett,[42] Katzumi [45] and Svartz and Brodd,[46] is that without sugar in the culture mediums Cl. Welchii produces no toxins. It is hard to resist drawing a parallel between these laboratory observations and the presence of toxic symptoms in some cases of intolerance for carbohydrates.

A serious objection to the theory of absorption and systemic influence of toxins from the Welch Bacillus is that it is very sensitive to acid.[47] Our quantitative bacteriologic studies, which failed to show an overgrowth of Cl. Welchii even in some severe cases with toxic symptoms (in the larger series), add a weighty argument against a direct causative relationship between intestinal infestation with this organism and toxic manifestations in our patients. Moreover, the absence of vascular hypotension among patients in the group with toxic symptoms is against Kendall's theory [8] that a histamine-like toxin produced by the Welch organism is responsible for the hypotension which is frequently seen in this syndrome.

In summing up, we believe that irritating and perhaps toxic products of fermentation materially contribute to the abdominal symptoms of intestinal intolerance of carbohydrate, and that among our patients there is a small but sufficient number who show that it is possible for the intestinal absorption of toxic substances to affect distant organs. As yet there is insufficient evidence to implicate any specific toxic substance or bacterial toxin. During the recent past so many conditions were blamed on "intestinal autointoxication" without convincing proof that a healthy skepticism on this subject is necessary. This, however, should not prejudice one against the possibility of toxic absorption from the bowel, if sufficient evidence in its favor can be presented.

TREATMENT

A therapeutic regimen consisting of three parts has been worked out over several years by one of us (T. L. A.). During the first period a strict limitation of carbohydrates is essential. The patient is permitted to eat with each meal one thin slice of toast or 2 tablespoonfuls of

45. Katzumi, Kajima: Beiträge zur Erforschung der Rauschbranderreger: II. Ueber Toxin und Antitoxin der Typus Foth und Kott und ihre besonderen Verschiedenheiten, Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**:185, 1923.

46. Svartz, N., and Brodd, C. A.: Recherches sur les propriétés hémolytiques du bacille de Welch-Fraenkel obtenu par culture du contenu intestinal, Acta med. Scandinav. **75**:450, 1931.

47. Zeissler, J.: Die Gasödeminfektionen des Menschen, in Kolle, W., and Wassermann, F.: Handbuch der pathogenen Mikroorganismen, Jena, Gustav Fischer, 1928, vol. 4, pt. 2, chap. 14, p. 1099.

macaroni or of a well cooked cereal. The intake of sugar is reduced to a minimum. The following are totally excluded from the diet: potatoes, rice, root vegetables, dried beans, peas, lentils, cabbage, cauliflower, Brussels sprouts, broccoli, peppers, cucumbers, onions, garlic, pickles, spices of all kinds and sweet milk. The patient is allowed ordinary amounts of meat, eggs, fish and cheese, but is advised that the last form of protein is preferable. Green vegetables are to be eaten cooked and puréed. Fruit must be taken either cooked or in the form of juices. There is no restriction of fats. Nuts, except peanuts, are permitted. On such a diet patients miss most keenly the bland carbohydrate articles of food, such as potatoes, bread and rice, which go with the highly flavored proteins. This difficulty is surmounted by advising them to eat every day some cottage cheese and gelatin, which are otherwise used only occasionally. The gelatin can be served with salads or meat and also in the form of desserts.

A special virtue is made of drinking fermented milk. Patients in the clinic are usually given buttermilk, while patients in private practice are asked to take acidophilus milk. Many patients at first develop an exacerbation of symptoms due to fermented milk, so that if the condition is at all marked it is advisable not to prescribe such milk for the first week or two and then to start with small amounts of it, gradually working up to a quart a day.

In addition, colloidal kaolin is prescribed in doses of from 8 to 15 Gm. three or four times a day between meals. Here, again, one must keep within the limits of individual tolerance. The patient must also be advised to keep the bowels open with liquid petrolatum by mouth and, if necessary, by olive oil retention enemas lest hard fecal concretions form from the kaolin. This regimen is to be followed in ordinary cases between two and six weeks.

During the second period carbohydrates, mainly milled starches, sugar and well cooked cereals, are gradually increased in the diet until normal proportions are reached. The administration of fermented milk and kaolin is continued as previously. The approximate duration of this regimen in favorable cases is about one month. Then if the patient is still free from symptoms or nearly so the third part of the treatment can be started.

During the third period an attempt at bacterial implantation is made by putting patients on acidophilus milk or, in case of intolerance, on 4 cc. of a standard culture of Bacillus acidophilus three times a day. The patient is also instructed to begin using lactose or lactodextrin at meal time, starting with a teaspoonful and working up to a tablespoonful. At the same time medication with kaolin is discontinued. Such a regimen should be followed for at least two months. After the administration of the B. acidophilus preparation is stopped, the patient continues to take lactose with meals indefinitely.

It is again to be emphasized that the administration of fermented milk, of kaolin and of lactose must be adapted to the individual case, and that successive steps in the diet should be prescribed only after the patient has been comfortable on the preceding regimen. We have several times seen enthusiastic interns force on a frail woman with an irritable bowel large amounts of fermented milk, kaolin or lactose, only to have the patient become worse. In the same cases a favorable response was obtained later by proceeding more cautiously.

The purpose of this diet is to limit the total amount of carbohydrates and to confine their absorption as much as possible to the upper part of the small intestine by excluding foods in which the starch is covered by a cellulose membrane. Such a diet decreases fermentation in general and is also directed against the excessive growth of carbohydrate-fermenting, spore-forming anaerobes. The advantage of casein over animal protein is that, according to the work of Cannon,[40] it encourages an aciduric flora. A number of vegetables which are well known formers of gas and which probably contain irritating substances in addition to starch are excluded from the diet.

Since Graham and Emery [48] and Hull and Rettger [22] showed that dietary changes even with the addition of large amounts of lactose do not influence the acidity of the intestine, fermented milk is given in order to lower the p_H of the intestinal contents by the direct addition of preformed lactic acid. A shift in the reaction of the intestine to the acid side is desirable, as has been stated previously, in order to limit the upward extension of the colonic flora in patients with insufficient gastric acidity. Torrey and Kahn [49] expressed the belief that an increase in intestinal acidity inhibits particularly the spore-bearing anaerobes, and Kendall, Day and Walker [50] demonstrated that patients with intolerance of carbohydrate benefit from soured milk, regardless of the organism which ferments the milk.

The efficacy of a commercial preparation of lactic acid in agar in two concentrations was compared in six cases with the action of fermented milk. The results were inconclusive. Since the cost of this preparation is much greater than that of buttermilk, its trial is indicated only in patients who are disinclined to take fermented milk.

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48. Graham, W. R., and Emery, E. S.: The Reaction of the Intestinal Contents of Dogs Fed on Different Diets, J. Lab. & Clin. Med. **13**:1097, 1928.

49. Torrey, J. C., and Kahn, M. C.: The Inhibition of Putrefactive Spore-Bearing Anaerobes by Bacterium Acidophilus, J. Infect. Dis. **33**:482, 1923.

50. Kendall, A. I.; Day, A. A., and Walker, A. W.: Chemistry of the Intestinal Flora of Man Containing Abnormal Numbers of Gas Bacilli, J. Infect. Dis. **38**:217, 1926.

Kaolin is prescribed for several purposes. As shown by Walker,[51] Dudgeon [52] and Braadfladt,[53] it removes large numbers of bacteria and, according to the belief of these workers, changes the fecal flora, at least in normal persons, to the aciduric type with almost total disappearance of gas bacilli. Furthermore, kaolin is an efficient adsorbent of toxic substances in the intestine. Finally, by coating the intestinal mucosa to which it clings tenaciously, kaolin serves as a barrier against mechanical as well as chemical irritants.

We are particularly interested to know whether the action of kaolin in removing bacteria from the intestine, which was also demonstrated by Braadfladt in vitro, is purely mechanical or whether it is a colloidal phenomenon. In the latter event, since practically all bacteria carry negative charges and since kaolin is also negatively charged in neutral and alkaline suspensions, acquiring a positive charge only in acid mediums,[54] it occurred to us that some substance positively charged in neutral suspension might prove more efficacious than kaolin. This would be of special importance in cases in which insufficiency of hydrochloric acid, by diminishing the acidity of intestinal contents, may interfere with the bacteria-removing action of kaolin. We performed a number of experiments in which the adsorptive ability of various electrically negative and positive substances were tried on suspensions of Cl. Welchii and B. coli with different p_H values. This work is not completed, but we have had hopeful indications in the use of barium sulphate, calcium carbonate and charcoal, in addition to kaolin.

If the action of kaolin and other compounds in removing bacteria is based on colloidal adsorption, the method of administration of these substances to the best advantage is not indifferent. And since the digestive tract can handle only a certain amount of inert foreign substance, it is particularly important to determine whether repeated moderate doses or a single large daily dose will produce the maximum effect.

Implantation of B. acidophilus is attempted because this organism increases the acidity of the intestinal contents by producing lactic acid and also because of its supposed antagonism to the growth of spore-forming anaerobes. Preparations of this organism need to be given only during the third period of treatment, because not until then is the

51. Walker, R. R.: Kaolin in the Treatment of Asiatic Cholera: Its Action and Uses, Proc. Roy. Soc. Med. **14**:23, 1921.

52. Dudgeon, L. S.: A Study of the Intestinal Flora Under Normal and Abnormal Conditions, J. Hyg. **25**:119, 1926.

53. Braadfladt, L. H.: The Effect of Kaolin on the Intestinal Flora in Normal and Pathological Conditions, J. Infect. Dis. **33**:434, 1923.

54. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, St. Louis, C. V. Mosby Company, 1930, p. 48.

diet favorable for its growth. To quote from Rettger,[55] "The ingestion of foreign bacteria alone, even in large numbers does not of itself bring about an elimination or displacement of the common intestinal micro-organisms. Vastly more important is the influence of diet especially milk and lactose." Porter, Morris and Meyer [56] demonstrated that B. acidophilus preparations may aid the establishment of an aciduric flora in children but that this influence is not great.

Simultaneously with the beginning of implantation therapy the patient is given lactose in order to create optimum conditions for B. acidophilus. The administration of this sugar must be started cautiously, because patients with this syndrome do not tolerate lactose well and often have a recurrence of their symptoms even with small doses. This was shown in a spectacular manner in two instances in which large amounts of lactose were prescribed by a physician on the strength of a laboratory report of "proteolytic flora." The reaction that followed can aptly be described as an "explosion."

As supplementary therapy, calcium carbonate in doses of 1 teaspoonful is given to patients with much abdominal pain or diarrhea. This drug brings relief, according to Porges and Esser [14] and Bokai,[30] by neutralizing butyric acid. We have also indications that, similarly to kaolin, it may remove bacteria from the intestine. The objection to the routine use of calcium carbonate lies in its neutralizing effect on the hydrochloric acid of the stomach, thereby reducing intestinal acidity.

Hydrochloric acid was prescribed for patients with achlorhydria, but it probably cannot be given in sufficient amounts to affect the intestinal acidity.

Diastase, as advocated by Hurst and Knott,[4] was tried repeatedly in refractory conditions but without success.

Heptyl-resorcinol was given a thorough trial in six patients because of its supposed effect on putrefactive micro-organisms,[57] but neither the amount of putrefaction nor the formation of gas in beef-heart medium was appreciably changed.

On the suggestion of Dr. G. B. Eusterman and Dr. J. L. Kantor that intolerance for carbohydrate may be a mild form of sprue, liver extract was given to three patients. These patients, who had not improved with other methods of therapy, also failed to respond to liver extract.

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55. Rettger, L. F.: The Influence of Milk Feeding on Mortality and Growth, and on the Character of the Intestinal Flora, J. Exper. Med. **21**:365, 1915.

56. Porter, L.; Morris, G. B., and Meyer, K. F.: Certain Nutritional Disorders of Children Associated with a Putrefactive Intestinal Flora, Am. J. Dis. Child. **18**:254 (Oct.) 1919.

57. Veader, L., and Feirer, W. A.: Di-Hydranol: Control of Intestinal Putrefaction in Man by Oral Administration of 2-4-Dihydroxyphenyl n-Heptane, Bull. Johns Hopkins Hosp. **48**:25, 1931.

Our latest venture in the treatment of this condition, directed mainly against flatulence, consists in the administration of vitamin B, on the theory that by increasing the tonus of the intestine we may improve the absorption of gases. In order to avoid simultaneous feeding of carbohydrate we have chosen vegex as the most suitable commercial preparation of vitamin B. Our results in a few cases have been encouraging but so far warrant no conclusions.

RESULTS OF TREATMENT

In a little more than one fourth (28 per cent) of fifty consecutive cases marked improvement of gastro-intestinal symptoms was recorded. The patients in this group recovered their ability to eat without trouble ordinary amounts of most carbohydrates with the possible exception of one or two articles of diet. Only two patients maintained that they could take all forms of starch in unlimited quantities and remain free from symptoms. These two, unfortunately, moved without leaving a forwarding address, so that we are unable to substantiate the permanence of their relief.

A little more than one half of the patients (54 per cent) showed partial improvement. In this group are included persons who are reasonably comfortable, but not well, as long as they restrict the amount and kind of carbohydrate foodstuffs in the diet. Most of these patients have periods of better tolerance to starches which, without change in the diet or other apparent reason, are followed by periods of exacerbation of symptoms. Such attacks respond to strict limitation of carbohydrates, and this again seems to increase their tolerance. These obscure fluctuations of tolerance for carbohydrate may be connected with the seasonal occurrence of some intestinal bacteria. Kendall, Day and Walker [50] claimed to have demonstrated such variations for Cl. Welchii in the stools of normal persons, and the same may be true of other microorganisms.

In addition, some of these patients of their own accord continue to take fermented milk indefinitely, while others cannot get along comfortably without kaolin. On the whole, patients in this group accept with more or less grace permanent dietary restrictions and achieve a higher level of comfort and activity. Perhaps a measure of their improvement is the fear with which most of them contemplate a return to a general diet.

About one fifth (18 per cent) of the patients derived no benefit from any treatment tried. All the patients in this group either had classic mucous colitis, characterized by numerous bowel movements with much mucus after nervous excitement, or passed copious amounts of mucus without outspoken attacks of diarrhea. It was also noticed in general

that treatment was less successful in patients who had noticeable amounts of mucus in the stools and in those who had periodic or chronic looseness of the bowels. The duration of the condition before treatment apparently has no prognostic significance.

No marked shift of the fecal flora to the aciduric type has been observed after the implantation of B. acidophilus even in patients who were able to tolerate moderate amounts of lactose (50 Gm. a day) over long periods. In this connection the question arises to what extent it is possible to change the intestinal flora in abnormal cases. Successful experiments of this nature reported in the literature were performed largely on healthy men or animals. In contrast to this is the observation of Torrey [10] on patients with typhoid fever that the degree of transformation of the intestinal flora by diet and lactose depends on the initial type of flora present. He found that when there is a definite putrefactive tendency the change extends only to the elimination of obligate putrefactive organisms and a moderate development of the aciduric types. With a more favorable initial flora he obtained striking changes.

Patients with toxic symptoms were relieved of their gastro-intestinal manifestations so long as they limited the amount of starches in their diet. Moreover, in all the patients with anemia the erythrocytes increased to well within normal limits, and albuminuria disappeared in all but one case. Some of the patients in this group have totally excluded all articles of food rich in starches for periods up to ten years, without any apparent harm.

SUMMARY

A common but not generally appreciated clinical entity, characterized by intolerance of carbohydrate, with complaints centering around marked meteorism, is the subject of the present investigation. Gastro-intestinal and systemic manifestations of this condition were studied in fifty consecutive patients. The more prominent local symptoms are gaseous distention with abdominal pain; excessive flatus; nocturnal colonic distress, and constipation, replaced in severe cases by chronic diarrhea. A background of asthenia, nervousness and vasomotor instability is prominent. In addition, a smaller group of patients had anemia, albuminuria and chronic choroidoretinitis, all probably of toxic origin.

Fermentation tests, quantitative studies of stools for Cl. Welchii, aciduric organisms and other features of the intestinal flora permit no consistent correlation with the clinical picture. Extension of the colonic flora into regions of the small intestine where unabsorbed carbohydrates are present and penetration of carbohydrate material into the colon are factors which favor excessive fermentation. Conditions interfering

with the resorption of gases from the intestine, such as loss of tonus by the bowel, also play a large part in the production of flatulence. Irritating organic acids formed during fermentation are probably partly responsible for the local symptoms. The systemic manifestations are probably due to the absorption of some toxic substances the formation of which is favored by the abnormal condition in the bowel.

Strict limitation of carbohydrates, especially starches, in the diet, together with the administration of fermented milk, and kaolin medication afford partial to complete relief in most cases. Coexisting mucous colitis is a complication which seriously interferes with the success of the therapy.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY

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Since this is the first review of neuropsychiatry to be published in the ARCHIVES OF INTERNAL MEDICINE, with others to follow annually, I shall not confine it to the last year but shall sketch somewhat broadly the ways along which advances have been made in the last several years. Physiologic and psychologic discoveries are considered important enough to be discussed here because they are either precursors of therapy or elucidators of empirical treatment. Successful new methods of treatment are few but will be emphasized because of their practical use to the physician. In a brief paper only a few topics can be discussed. For those who wish to read more extensively, two books in English are recommended: "The Problem of Mental Disorder," a collection of twenty-five current points of view, edited by Madison Bentley,[1] and "Recent Advances in Neurology" by Brain and Strauss.[2] In German the monthly review journal *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* is most helpful.

THE PSYCHOGENIC ORIGIN OF SOMATIC LESIONS

Improvement in the cooperation between internist and psychiatrist has been conspicuous recently because of the better understanding of psychosomatic interrelationships. The paper by Moschcowitz[3] is an excellent example. He gave instances of the definite causal relation between reiterated emotional reactions and well established anatomic lesions in such diseases as exophthalmic goiter, essential hypertension, gastric ulcer and mucous colitis. That emotion may cause profound functional changes is acknowledged. Moschcowitz expressed the belief that prolonged abnormal function may result in profound anatomic change. Hitherto, pathologists have not recognized that such a sequence exists, because of the domination of the belief that morbid anatomy comes first and abnormal function follows. Among physiologists, Cannon[4]

1. Bentley, M., and Cowdry, E. V.: The Problem of Mental Disorder, New York, McGraw-Hill Book Company, 1934.

2. Brain, W. R., and Strauss, E. B.: Recent Advances in Neurology, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1934.

3. Moschcowitz, E.: New England J. Med. **212**:603, 1935.

4. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear, and Rage, ed. 3, New York, D. Appleton & Company, 1929.

has led the way and given experimental proof that emotions change bodily functions.

The Josiah Macy Jr. Foundation is to be congratulated on having aided H. F. Dunbar [5] in compiling an extensive survey of the literature on emotions and bodily changes. In a general way most physicians believe that the mind affects the body, but actual data have not been easily available. This book gives literally hundreds of specific instances from the fields of endocrinology, metabolism, cardiology, gastroenterology, dermatology and the like. For example, well authenticated cases are given of hair turning white or falling out after a severe fright. Three different experimenters have produced blisters on the skin by hypnotic suggestion; thus it is easier to accept the excellent clinical evidence for the occurrence of spontaneous hysterical ecchymoses. Cases are cited in which fever of psychogenic origin has been carefully observed and then cured and reinduced by hypnotic suggestion. The gastro-intestinal disorders produced by emotional stress are remarkably common and varied—all the way from the psychic influence on salivary secretion, which is common knowledge, to the psychogenic hypermotility and hypersecretion which lead to peptic ulcer. The evidence for this last stage, the development of the ulcer, is less direct, but the number of observations is impressive. One could go on and on quoting anecdotes from this book; the lesson to be learned, therefore, is that these occurrences are not extraordinary but can be seen at all times by the physician.

The use of the word "functional" to denote "psychogenic" or "emotional" is to be deplored. Even in Dunbar's book it is misused. Jelliffe [6] put the case well by saying: "I talk of 'reversible and irreversible' organic changes, never of 'organic' changes. Organic changes are always taking place in all functioning organs. Any one should know that; whether within the physiological range and whether reversible or not is the important consideration." Two writers in Bentley's [1] book "The Problem of Mental Disorder" have stressed the importance of the definition of such terms. Under the heading of "A Dichotomy in Psychiatry and Medicine: 'Organic' and 'Functional' " [7] one reads: "I do not know of any function without structure . . . if we mean by the term 'functional disease' that etiology and pathology are unknown, it would

5. Dunbar, H. F.: Emotions and Bodily Changes, New York, Columbia University Press, 1935.

6. Jelliffe, S. E.: Arch. Neurol. & Psychiat. **30**:239 (July) 1933, in reply to a book review on his Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis, Washington, D. C., Nervous and Mental Disease Publishing Company, 1932.

7. Bentley and Cowdry,[1] p. 34.

be better to say so. The medical psychiatrist . . . *has no use for the metaphysics which separate mind and body.*" Later in the book [8] it is stated:

The great stumbling block to effective cooperation between physician and psychiatrist is the widely and complacently accepted idea that all diseases can be divided into two categories, and classified as either "functional" or "organic." It is extraordinarily difficult to explain to a man trained in the school of pathological anatomy that his criterion for calling one disease organic and another functional is entirely artificial, that the deciding factor is the instrument he happens to use to record the abnormality of the organ under observation. Just at present the instrument most relied upon is a microscope with a limit of magnification of about twelve hundred diameters. Suppose that some physicist tomorrow invents a microscope with a much greater useful magnification. At once abnormality may be seen where none was previously visible. But why confine ourselves to the microscope? Certainly there are other ways of recording abnormality of the human organism besides visual observation of fixed and sectioned tissue. For example, the spectroscope may show that a certain type of sugar is found in the urine of an athlete before a contest. This is an observation which may be recorded photographically; it is a phenomenon which can be shown to occur regularly; by chemical methods the sugar may be estimated quantitatively. The average histopathologist, nevertheless, will strenuously maintain that there is no organic pathology in this anxious athlete, and that the disease is "merely functional." What the histopathologist really means is that after an autopsy on this athlete no lesion would be visible in stained sections of tissue, with a microscope of the type used in the year 1934.

To attack the subject from another angle one has only to consider the numerous diseases where chronic functional disturbance leads to organic lesion. It is known that sudden fright may precipitate Graves' disease, with exophthalmia, enlarged thyroid gland, and increased metabolic rate. A somewhat more complicated situation was presented to me by a patient who came to the clinic with the mental, neurological, and dermatological symptoms of pellagra. At autopsy, the nerves, cord, and brain showed typical neuronal lesions. Yet primarily, as the history showed, the patient's trouble was fear. This had early made him a recluse, later led to restriction of diet and eventually to pellagra. In this case there was certainly gross and microscopic organic pathology. But who can draw a line showing where "mental" cause ceased and "physical" cause began?

It may seem pedantic to expatiate upon the impossibility of drawing a line between "organic" and "functional," but experience shows that it is necessary to emphasize that no such line can logically be drawn. If it is drawn arbitrarily, its position is ordained by the point to which technology has advanced in that year. It depends on what kind of a "scope," "graph," or "meter" is used by the observer. In other words, the line between organic and functional (and between physical and mental) is an artefact. . . . Structure and function are inseparable.

THE HUMORAL TRANSMISSION OF NERVOUS IMPULSES

The discovery of humoral agents in the transmission of nervous activity from nerve to muscle is a physiologic advance which probably has momentous implications for neuropsychiatry. Loewi was the first

8. Bentley and Cowdry,[1] p. 111.

to demonstrate clearly the chemical transmission of nervous effects by showing that the effect of vagal stimulation on a frog's heart is due to an agent which is formed in the muscle and then circulates in the blood. Sir Henry Dale [9] has almost certainly identified this substance as acetylcholine. Another substance which transmits effects like those caused by stimulation of the sympathetic system has been found by Cannon.[10] This has been named sympathin and has properties that suggest a close relationship to epinephrine. It is clear that the heart is controlled by the opposing effects of these two chemical substances liberated among the fibers of the cardiac muscle. Furthermore, recent work from Dale's laboratory indicates that every ordinary motor nerve impulse to a fiber of a voluntary muscle produces a tiny charge of acetylcholine in contact with the receptive plate of the muscle fiber. In his address at the opening of the Lilly Research Laboratories in October 1934 Dale said:

> For the whole of the peripheral nervous system, then, we seem to be in sight of knowledge enabling us to describe the transmission of effects, from nerve fibers to receptive cells, in terms of precise chemistry. And the vast and complex problem of the central nervous system still remains. It will be strange, indeed, if knowledge of this kind, expanding just now with such unexpected rapidity, does not eventually have some effect, if only an indirect one, on practical therapeutics.

Optimistic though this may seem and possibly open to the criticism that the evidence is incomplete and not corroborated by other workers, the discoveries are certainly important for those interested in nervous and mental disease.

Some corroboration comes from the zoologic researches of Parker.[11] He observed in certain fishes two classes of nerve fibers to the chromatophores, one expanding the chromatophore and the other contracting it. These apparently act by secreting neurohumors at the nerve terminals. If the blood from a flat fish, dark in consequence of a long sojourn on a dark background, is withdrawn and injected into a light fish, a dark spot due to the expansion of the chromatophores appears near the site of the injection; vice versa, a light spot may be produced on a dark fish.

MYOPATHY

In the field of muscular dystrophy and atrophy some order seems to be emerging from the chaos of syndromes. There appear to be three groups [12] of primary atrophies. The first is made up of sporadic

9. Dale, H. H.: Science **80**:343, 1934.

10. Newton, H. F.; Zwemer, R. L., and Cannon, W. B.: Am. J. Physiol. **96**: 377, 1931. Cannon, W. B., and Bacq, Z. M.: ibid., p. 392.

11. Parker, G. H.: Humoral Agents in Nervous Activity, New York, The Macmillan Company, 1932.

12. Aring, C. D., and Cobb, S.: Medicine **14**:77, 1935.

diseases: amyotonia congenita, progressive muscular atrophy and amyotrophic lateral sclerosis. These are not familial. The second is the group of hereditary myopathies in which lesions are almost entirely in the muscles but associated with a significant amount of abnormality in the endocrine glands. In this group creatine metabolism is most abnormal.[13] The third is a group of strongly inherited diseases due to pathologic conditions in certain tracts of the spinal cord. These are true system diseases and are related to many nervous disorders which are not commonly associated with muscular atrophy or dystrophy. It is only in the second group of diseases that progress is being made in treatment. Here the therapeutic use of amino-acetic acid[14] seems to result in improvement in some patients. The supposition is that in this group of myopathies the body has lost its ability to utilize creatinine. Ephedrine has been found beneficial, especially for myasthenia gravis,[15] and it also has been used as an adjunct to treatment with amino-acetic acid. Most helpful of all, however, is the recent use of the di-methylcarbamic ester of m-oxyphenyl tri-methyl ammonium methylsulfate[16] for myasthenia gravis. It gives immediate and striking relief, but the effect apparently lasts for only a short time. Experimental investigations suggest that myasthenia is due to a delayed restoration of normal chemical relations at the myoneural junctions after fatigue. This delay interferes with the passage of excitation from a motor nerve to the end-plate of a muscle. It is possible that drugs of the physostigmine group act on acetylcholine at the end-plate.[17]

ELECTRO-ENCEPHALOGRAPHY

The technic of neurophysiology has been so much improved lately by the advances in physics that now, by the use of the radio amplifier and the oscillograph, the investigator of electrophysiology can record changes in electrical potentials of the intensity of a thousandth of a volt and of a duration of a ten thousandth of a second. These are recorded photographically. Such an armamentarium makes possible the recording of minute changes in potential (action currents) in the brain, even through the skull. Records of these changes are called electro-encephalograms, and they show as wavelike variations in the voltage; hence the popular name "brain waves." Experiments have shown that there is almost constant cerebral activity, greater in the association areas of the cortex than in the projection areas. Special regions of the cortex, such as the visual area in the occipital lobe, can be made

13. Milhorat and Wolff: Internat. Neurol. Cong., 1935, abstr. vol., p. 55.
14. Milhorat, A. T.: Deutsches Arch. f. klin. Med. **174**:487, 1933.
15. Edgeworth, H.: The Effect of Ephedrine in the Treatment of Myasthenia Gravis: Second Report, J. A. M. A. **100**:1401 (May 6) 1933.
16. Pritchard, E. A. B.: Lancet **1**:432, 1935.
17. Pritchard, E., and Blake: Internat. Neurol. Cong., 1935, abstr. vol., p. 103.

to produce complex waves by stimulation of the optic nerve.[18] The administration of drugs and the induction of anesthesia modify these responses. During sleep[19] much activity goes on. In the early part of a period of sleep there are series of waves which are fairly regular and gradually become lower in amplitude and more random in type. When the subject is aroused the waves immediately become more numerous, regular and larger. This change seems to be in relation to the changes in the level of consciousness. In epileptic patients[20] special forms of waves have been observed preceding attacks of both petit mal and grand mal. Most interesting are smaller waves of a similar form which sometimes occur in these patients without being followed by a clinical seizure, as if a subliminal fit were being recorded. The diagnostic possibilities suggested by this work are great.[21] The limitation of the method seems to be the complexity of the brain itself; too many and too complex processes are going on at once. Studies of seizures, of states of consciousness and of special senses are obviously important, but it seems improbable that correlations with complex "mental" changes or psychologic variations can ever be made by this method.

EPILEPSY

Marked progress has been made in the understanding of epilepsy. At the International Neurological Congress in London in July 1935 a whole session was given over to this subject, and the many papers presented accurately reflect a new point of view. Abadie (Bordeaux) stated clearly that the time is past when epilepsy can be considered to be a disease; it is a syndrome or manifestation of a lesion of the central nervous system. The old doctrine of idiopathic epilepsy has been entirely abandoned. Abadie even said that epilepsy is always an acquired disorder, never inherited. With that statement many would not agree, for although inherited epilepsy is much less common than most textbooks would lead one to believe, convincing evidence is available that it may be inherited either alone[22] or with migraine.[23] A fine paper by Lennox (Boston) summed up the physiologic pathogenesis so well that the abstract is largely quoted:

> In patients having frequent seizures, certain alterations of physiological processes in the brain (water balance, acid-base balance, oxygen or blood supply)

18. Bishop, C. H., in Bentley and Cowdry.[1]

19. Loomis, A. L.: Science **82**:198, 1935.

20. Gibbs, F. A.; Davis, H., and Lennox, W. G.: Studies in Epilepsy: Alterations in the Electro-Encephalogram Occurring in Epilepsy and in Other Conditions Characterized by Loss of Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935.

21. Kornmuller, A. E.: Fortschr. d. Neurol., Psychiat. **7**:391, 1935.

22. Goldstein, M.: Internat. Neurol. Cong., 1935, abstr. vol., p. 34.

23. Ely, F. A.: The Migraine-Epilepsy Syndrome: A Statistical Study of Heredity, Arch. Neurol. & Psychiat. **24**:943 (Nov.) 1930.

modify the frequency of seizures. Alkalosis induced by overventilation or by ingestion of alkali tends to increase seizures; acidosis induced by fasting, by a ketogenic diet, by ingestion of acids or acid-forming salts, by breathing carbon dioxide or by muscular activity tends to decrease seizures. The total blood flow through the brain, as measured by a thermo-electric blood-flow recorder inserted in the internal jugular vein, does not show reduction immediately before the seizure except when the seizure is induced by overventilation. These observations prove that generalized cerebral anemia is not the cause of spontaneous seizures. The total oxygen consumption and oxygen content of the blood are normal.

An acute cerebral anoxemia was produced in two ways: By breathing of pure nitrogen and by induction of orthostatic syncope consequent on ingestion of sodium nitrate. Results differed in patients having grand mal and those having petit mal seizures. Out of twenty grand mal cases rendered unconscious by one of these procedures, only one experienced his usual type of grand mal seizure. In thirteen patients having frequent petit mal, with or without mild localized convulsive movements, the patient's usual seizure was readily and consistently induced by an induction of anoxemia or cerebral anemia. Usually the degree of anoxemia was insufficient to produce unconsciousness in the normal individual.

The electro-encephalogram shows that petit mal seizures are invariably preceded or accompanied by a burst of electrical potentials about ten times the voltage and about one fifth the frequency of the patient's usual potentials. When clonic movements are present, they are synchronous with these large waves; similar voluntary movements are unattended by differences in electrical potentials. The form of the large waves is individual for each patient. Furthermore, the electro-encephalograms of patients, taken between attacks, show small disturbances of rhythm suggestive of larval or sub-threshold seizures. Induction of alkalosis by hyperpnoea, of anoxemia by nitrogen breathing and of cerebral anemia by fainting (in both patients and normal persons) also causes waves of increased magnitude and decreased frequency. With increasing alkalosis or anoxemia, these currents become larger and larger until the patient's typical form of action currents (and the accompanying seizure) appears.

At the International Neurological Congress Minkowski (Zurich) described the pathology of the brain in persons subject to seizures. He said that some pathologic change is always observed if the histologic work is careful and thorough enough. Ulrich (Zurich) described a successful method of bromide therapy in which the dosage was controlled by careful quantitative estimations of the amount of bromide in the blood. Penfield (Montreal) spoke on surgical therapy. He pointed out that a focal lesion of the brain is often present even in cases of "idiopathic" epilepsy. When the history, the presence of neurologic signs or the pattern of the attacks suggests the possibility of a focal lesion an encephalogram should be made. Also, an attack should be observed even if it has to be induced. At operation the cortex should be investigated by electrical stimulation. The lesions which lend themselves to surgical treatment are scars uniting the meninges to the brain and areas of cerebral atrophy. Penfield said that of twenty-two patients treated by radical excision of a meningocerebral cicatrix, ten had remained free from attacks and seven were much improved. In

twenty-two additional cases radical excision of areas of focal atrophy and focal cerebral cicatrix had been performed; nine of these patients were free from attacks, and seven were improved.

The treatment of epilepsy by means of hypodermic injections of acetylcholine has been tried by several investigators with apparently beneficial results.[24] The theory is that since cerebral vascular spasm may start the attacks, a vasodilator substance may prevent them. The mistake in all such arguments lies in the fact that epilepsy has no one cause; it is a symptom that may be produced by any one of fifty or more pathologic conditions. Some fits doubtless are due to spasm of cerebral arteries, but before therapy is instituted the pathogenesis of the seizure in each case should be carefully studied, and treatment appropriate to that particular case should be given. Generalizations about epilepsy are useless.

MIGRAINE

Much investigation into the cause of migrainous headache has been carried on during the last three years. The excellent review by Riley [25] in 1932 summed up the knowledge to that date. There has been a sad lack of autopsy material. Physiologic researches have fared better, and it has been shown that the walls of the meningeal vessels are sensitive and that changes in pressure which distort these walls cause headache.[26] Furthermore, ergotamine tartrate has been found to be effective in relieving and aborting attacks of migraine [27] in from 40 to 90 per cent of cases.[28]

TREATMENT OF DEMENTIA PARALYTICA

Experience is fast accumulating that proves the worth of the fever treatment of neurosyphilis. With careful handling a good remission with return to work is to be expected in 40 per cent of patients with an early stage of the disease, and an additional 20 per cent show distinct improvement. Infection with malaria is still the method most used, but typhoid vaccine is effective and advisable for patients not physically fit to withstand malarial infection.[29] A marked increase in the occurrence of hallucinations has been reported by several authors during fever therapy.[30] Hyperpyrexia induced by other methods is becoming

24. Stander, K. H.: Fortschr. d. Neurol. & Psychiat. **6**:419, 1934.
25. Riley, H. A.: Bull. Neurol. Inst. New York **2**:429, 1932.
26. Clark, Hough and Wolff: Internat. Neurol. Cong., 1935, abstr. vol., p. 47.
27. Lennox, W. G.: New England J. Med. **210**:1061, 1934.
28. Kennedy, F.: Bull. New York Acad. Med. **11**:511, 1935.
29. Schnitker, M. T.: Treatment of Dementia Paralytica with Typhoid H Antigen Vaccine: Report of Twenty-Five Cases in Which Fever Therapy Combined with the Administration of Tryparsamide Was Used, Arch. Neurol. & Psychiat. **31**:579 (March) 1934.
30. Pap, Z.: Arch. f. Psychiat. **102**:57, 1934.

more effective. Diathermy [31] has given improvement in as many as 50 per cent of cases, but the danger of burns is ever present. Hot baths have been used but are too exhausting to the patient. Hot-air cabinets are effective. Perhaps the safest and simplest device is the electric blanket,[32] which is easily controlled and keeps the patient's temperature at from 104 to 105 F. by mouth for several hours without discomfort.

Various methods of radically changing the level of consciousness of a psychotic patient have been used in the treatment of mania, depression and catatonic stupor. A mixture of the di-ethylamine salts of di-ethylbarbituric acid and allylisopropylbarbituric acid,[33] paraldehyde, amylene hydrate, chloral [34] and other drugs have been used. The patient is kept in a prolonged narcotic state, sometimes for two weeks. The amount of improvement obtained is not impressive. Amytal also has been used to remove inhibition and cause the patient to talk about his repressed fears during the excited stage preceding sleep or during the period of awakening. It seems to have been an aid in hastening psychotherapy in many cases. The use of inhalations of carbon dioxide and oxygen to arouse a patient from stupor has had dramatic results, but although the improvement is remarkable, it appears to be short lived. As a result of this experience prolonged sojourn in an oxygen chamber has been tried on the basis of the theory that there is a state of cerebral suboxidation in dementia praecox. So far the results have been disappointing.

MULTIPLE SCLEROSIS

As long as the pathogenesis of multiple sclerosis remains unknown, no good results of treatment can be expected. The spirochetal and virus theories of etiology have been discredited. Various other explanations of the disease are being brought up; exacerbations of the symptoms have been found to be related to barometric changes,[35] and in fifty-nine of eighty-nine patients with multiple sclerosis a myelolytic agent has been isolated from the urine.[36] The theory that seems to fit most clinical and pathologic facts is the one proposed by Putnam [37] on the basis of several years' experimental work. He expressed the belief that

31. Graham, N. B.: Brit. J. Phys. Med. **8**:157, 1934.

32. Epstein, S. H.: New England J. Med. **212**:611, 1935.

33. Ström-Olsen, R., and McCowan, M. L. M.: J. Ment. Sc. **80**:658, 1934.

34. Cloetta, M., and Maier, H. W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:146, 1934.

35. Petersen, W. F., and Milliken, M. E.: Mental and Nervous Diseases, in The Patient and the Weather, Ann Arbor, Mich., Edwards Brothers, Inc., 1934, vol. 3.

36. Weil, A.: Internat. Neurol. Cong., 1935, abstr. vol., p. 53.

37. Putnam, T. J.: Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935; Internat. Neurol. Cong., 1935, abstr. vol., p. 51.

multiple sclerosis and certain forms of acute disseminated encephalomyelitis represent different stages and degrees of the same process. Both conditions have been stimulated in animals by the use of minute doses of tetanus toxin; a series of lesions resembling encephalitis in acute stages and sclerotic plaques when chronic have been produced in animals by the obstruction of cerebral venules. These results agree with the histologic observation of thrombi in the venules of human beings. Moreover, Putnam has observed a peculiar lability of the coagulation of the blood in patients. Thus it seems that one of a number of infectious or exogenous factors may activate the clotting mechanism to an abnormal degree, with the resulting formation of thrombi in the venules and of plaques of demyelinization about them. Such an explanation at present gives no specific indication as to therapy. It strengthens the conservative belief, however, that rest in bed during an exacerbation and an open-air regimen with much rest and sunshine between attacks, combined with a careful search for and removal of foci of infection, comprise the best treatment at present.

PSYCHONEUROSIS

In the history of medical research one finds over and over again that progress in the knowledge of the pathogenesis of a disease and in the treatment of a disease is made only after the disease can be reproduced in laboratory animals. It is therefore encouraging to learn that Pavlov has been able to reproduce in dogs psychologic conflicts which make them behave rather like persons suffering from minor psychoses ("neuroses"). He was able repeatedly to cause a state of "pathologic inertness," which he thought resembled human obsessional neurosis. The production of abnormal mental states in dogs is an important advance, but his speculative discussion of the type of psychopathology and the comparison with syndromes in human beings seem to me farfetched. Corroboration of Pavlov's experiments is already available from Liddell's [38] laboratory at Ithaca, where for eight years sheep have been observed with an "enduring derangement of behavior" resulting from "a conditioning routine" to which they could not adequately adjust themselves. Bromide and endocrine therapy have been tried on these "neurotic" animals with beneficial results.

Psychoanalysis continues to be used more and more for the treatment of the minor psychoses. Even the opponents of the freudian school admit that the method has one great advantage: the analyst starts by explaining to the patient that treatment will take at least a year and that success will depend on the patient's work, not that of the analyst. Thus the long and arduous task of reintegrating a per-

38. Liddell, H. S.; Anderson, O. D.; Kotyuka, E., and Hartman, F. A.: Am. J. Physiol. **113**:87, 1935.

sonality is begun with the shoe on the right foot. With too many of the shorter methods the patient starts out optimistically but is disappointed after a few months. The latest book by Freud,[39] entitled "New Introductory Lectures on Psychoanalysis," is a continuation and elaboration of his twenty-eight lectures published in 1917. There is a good chapter on education, in which he says that in a short span of time the child has to attain instinctual control and social adaptation and that much of this must be forced on him. The function of education is "to inhibit, forbid and suppress." One must steer between "the Scylla of giving the instincts free play and the Charybdis of frustrating them." The chapter entitled "Revision of the Theory of Dreams" impresses me as being a valuable contribution; certainly in this field the author has given to psychology and psychiatry a new way of understanding primitive thinking—"grammarless speech" and "the raw material of thought." The dogmatic interpretation of symbols, however, and the insistence on the thesis that "all dreams are wish fulfilments" are not easily accepted. There are too many positive statements; words like "absolutely certain," "inevitable" and "always" appear too often. In a discussion of the reaction of such a highly organized biologic unit as man such dogmatic statements are simply inaccurate. The book is written with artistry, and many passages show such keen insight and almost inspired intuition that they take hold of the rapid reader and convert him to the author's point of view. Careful reading, however, leaves the impression that Freud is a great man, certainly, an artist and a philosopher with an extraordinary intuitive faculty. He has probably made some remarkably shrewd guesses, which cannot be proved or disproved for many years to come. He weaves theories on weak evidence and elucidates aspects of human behavior that have heretofore been inexplicable. He sees deep into human nature. All great authors have done this, and some philosophers, but it is not science.

39. Freud, S.: New Introductory Lectures on Psycho-Analysis, translated by W. J. H. Spott, New York, W. W. Norton & Company, Inc., 1933.

Book Reviews

Blood Groups and Blood Transfusions. By Alexander S. Wiener, A.B., M.D., Brooklyn. Price, $4. Pp. 220, with 41 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This book brings together in a readable form practically everything that is known today about blood groups and the bearing that the subject has on the general biologic problem of the individuality of blood of different persons and animals. Although knowledge about such matters is but thirty years old and Wiener has by no means attempted to include all the references to literature, he has referred to considerably more than five hundred articles, monographs and books.

The author deals with the technic of detecting the four major groups, O, A, B and AB, some rather definite subgroups and the agglutinogens M and N, giving a preference, when routine groupings are done, to the Landsteiner method when a large number of serums are to be examined and to the slide method for testing one or two specimens. The various properties of the four groups are discussed, and the sources of error in grouping are clearly set forth. There follows a section dealing with the history of blood transfusion, the selection of donors and indications for and reactions to transfusions. Outside of definite incompatibilities, gross errors and accidents, no definite information is presented to explain the low grade post-transfusional reactions seen by all those who do many transfusions. The author apparently leans toward the citrate method but gives a discussion of all the methods in common use, pointing out the fact that the citrate method does not, in the hands of those experienced, produce more reactions than the direct methods. He could have expanded his criticism of certain apparatus for direct transfusions that are on the market, in particular, their failure to protect the donor adequately.

The most important sections deal with the inheritance of blood groups and other peculiarities of blood. The discussion is elaborate and mathematical. Bernstein's theory of three allelomorphic genes, A, B and R, is supported, and the evidence on which this argument is based is presented.

The anthropologic investigations are of considerable interest, and tables containing valuable information are numerous. It is noted that factor A, although decreasing from the West to the East, never becomes rare, whereas factor B becomes rare among western people. Theories for this are offered. Other chapters deal with groups in animal blood and the relation of the distribution of groups to clinical diagnoses, a field which has been, for the most part, nonproductive.

The final chapter deals with the medicolegal aspect of the subject, clearly setting down the backwardness of American courts in accepting such scientific evidence and the obvious usefulness of blood groups in settling many matters of dispute involving parentage and other matters. As yet, no record in a judicial decree in which grouping has been mentioned as the basis of the court's decision is available. A final warning is sounded that one who would appear in a court as an expert in such a case should be not only competent but well fortified by carefully performed tests and should have a vast experience in the study of biologic differences in human beings.

As a whole, the book is practical and clear, with enough detail to save the reader much time in looking up original material.

Radiologie clinique du tube digestif: I. Estomac-duodénum. By Pierre Duval, J. Ch. Roux and Henri Béclère. **Part 1: Estomac. Part 2: Duodénum.** Second edition. Cloth. Price, 330 francs. Pp., part 1, 252; part 2, 122, with 514 illustrations and 516 drawings. Paris: Masson & Cie, 1935.

The first edition of this work appeared seven years ago and was exhausted in about eighteen months. This, the second edition, was inspired by the advances

that have taken place in the roentgenology of the alimentary canal, especially those resulting from more punctilious demonstration of the mucosal relief, and the internal topography is given particular attention throughout. Although the work is essentially an atlas with profuse and excellent illustrations, the text is nevertheless amply explanatory, and the employment of drawings to elucidate the roentgenograms adds to its instructiveness.

After presenting the normal stomach with its variants, anomalies, functional alterations and displacements by extrinsic cancer, the intrinsic diseases of the viscus are discussed individually and, for the most part, thoroughly. The normal duodenum and the duodenum with a pathologic condition are handled similarly.

Although in the main the work follows conventional lines, a few surprises await the reader. Of gastritis, for example, the authors state that it is impossible at this time to describe the roentgen expression of this disease and that previous descriptions have been given without histologic controls. Continuing, the authors point out that the normal gastric mucosa is constantly mobile, with multiple and infinitely variable aspects, that Montier has never been able to establish any correspondence between the roentgen and gastroscopic appearances of the rugae in gastritis and that from histologic studies the authors have found that the roentgen images of healthy and profoundly affected mucosa are indistinguishable. Likewise, the authors hold that gastric syphilis has no pathognomonic roentgen signs and that the examination is incapable of contributing any information whatever to the etiologic diagnosis. And this from France whose syphilologists excel those of the world!

Other notable features of these volumes are the excellent chapter on the stomach after operation; absence of any reference to duodenitis, although periduodenitis is discussed at length, and the demonstration and differential criteria of the ampulla of Vater.

In the prospectus it is stated that the pupils of Professor Duval and the editors will be proud if foreign readers will say of this work that by its method and clarity of exposition the book is "very French." Their pride is warranted, but if any one conjectures that the work is prolix or imaginative he will be surprised to find that it is terse and extremely conservative. Any American radiologist who can read French at all will be able to understand the text and will derive pleasure and profit from the possession of this new contribution.

Klinik und Therapie der Herzkrankheiten. By Dr. D. Scherf, Assistant in First Medical University Clinic, Vienna. Price, 6.60 marks. Pp. 210, with 10 illustrations. Berlin: Julius Springer, 1935.

This is a delightfully practical booklet summarizing for practicing physicians the essential features of the short course in cardiology given each year in the First Medical University Clinic at Vienna. This course, one gathers, is very brief and solely for the benefit of physicians in general practice who wish to brush up on new methods of treating the common cardiac disorders that are seen most frequently.

Scherf states in his preface that there is no lack of good textbooks on heart disease to which any one can refer. His aim is not to attempt a new textbook but instead to set down as best he can the essentials of recent progress in cardiology and, especially, of progress in the art of making persons with heart disease as comfortable as possible.

He has little to say of electrocardiography and the roentgen rays, of congenital heart disease or of acute or subacute bacterial endocarditis. On the other hand, he has a great deal to say regarding the clinical picture of chronic cardiac decompensation: breathlessness, paroxysmal dyspnea of various types, chronic passive congestion and edema.

He is interested in describing the physical signs of the various valvular lesions and how accurate a diagnostician an intelligent observer can become if he is willing to train his eyes, hands and ears. He also lays proper emphasis on angina pectoris and disorders of the heart muscle.

About a quarter of the volume is devoted to therapy, for instance, to the proper and varied use of digitalis or its derivatives and morphine, with comments on the diuretics, the therapeutic use of bleeding and the intravenous injection of hypertonic dextrose solution. There is an excellent section on the management of cardiovascular syphilis, with due warning against the overenthusiastic use of arsenic without proper preliminary preparation, and another on the question of the proper type of diet for patients with heart disease.

At the end of the book is a comprehensive table of contents with page references so that one can quickly look up anything covered in the subject matter. There are practically no references to the literature, for the book is written as though the author were talking to his students, giving them the benefit of his own ideas and experience. On the whole, the monograph is a highly personal one, excellently written, and should prove a great boon to those for whom it was intended.

The Relation Between the Vitamin B Requirements and the Relative Quantity of Proteins, Fats and Carbohydrates in the Diet. (In Danish, with a summary in English.) By Dr. P. Vogt.-Møller. Pp. 165. Copenhagen: Levin & Munksgaard, 1934.

This monograph is a detailed account of a well controlled and extensive experiment (on mice) to determine whether the optimum requirements of the different vitamin B factors (B_1, B_2, B_4) vary with the relative quantity of three energy foods (proteins, fats, carbohydrates) in the diet. The criteria used were: growth, longevity and specific symptoms of avitaminosis. In the basal or standard diet protein (purified casein) made up 31 per cent; purified rice starch, 38 per cent, and Crisco, 22 per cent. To these were added: cod liver oil, 2 per cent of the diet; a mixture of sodium chloride, 7 per cent, and 1 drop of wheat germ oil daily.

In the high fat diet Crisco replaced starch entirely and made up 50 per cent of the diet, and the protein was raised to 39 per cent. In the high carbohydrate diet fat was eliminated, the rice starch raised to 70 per cent and the casein reduced to 25 per cent. Two diets high in protein were used. In one the 69 per cent casein was supplemented by 22 per cent Crisco; in the other 84 per cent casein was supplemented with 11 per cent rice starch. The calories per gram of diet remained essentially the same.

The results show that in mice, with the type of diets used, the minimum and optimum requirements of vitamin B_1 and B_4 increase with the increase in the carbohydrate fraction in the diet. The same relation obtains between vitamin B_2 and the fat in the diet. The results with diets high in protein were less conclusive, but indicated that the higher the protein content the greater the amount of vitamin B_2 necessary to prevent the development of pellagra. It is of interest to note that these and other studies have verified, in part, the original theory of Dr. Ejkman, that beriberi is due to chronic excess of starch in the diet.

Illustrative Electrocardiography. By Joseph H. Bainton and Julius Burstein. Price, $5. Pp. 258, with 100 plates. New York: D. Appleton-Century Company, Inc., 1935.

This is really an atlas of electrocardiography illustrating a great variety of normal and abnormal tracings with brief explanatory notes. Within the limits of such a project the execution is excellent; one wonders, however, whether any real purpose is served, since the expert is familiar with all this material, and the physician who is inexperienced can hardly train himself by the atlas method. However, for the physician who wishes to have at hand good illustrative curves of the various disorders of the cardiac mechanism for ready reference the book should be very useful.

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